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United States Environmental Protection Agency
Office of Pollution Prevention and Toxics

TOLUENE
(CAS Reg. No. 108-88-3)

PROPOSED ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

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Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

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EXECUTIVE SUMMARY

Toluene is a ubiquitous substance that is widely used as a raw material in the chemical manufacturing industry, as an additive in gasoline to increase the octane level, and as a solvent in lacquers, paint thinners, glue, and other compounds. The odor threshold for toluene ranges from 0.16 to 37 ppm for detection and 1.9 to 69 ppm for recognition; the odor is not unpleasant. Toluene is readily absorbed from the respiratory tract and distributed throughout the body, accumulating in tissues with high lipid content. Toluene is a CNS depressant and, at high concentrations, is irritating to the eyes. Other toxic effects observed in humans include renal toxicity, cardiac arrhythmias, blood dyscrasias, hepatomegaly, and developmental abnormalities. A considerable amount of human and animal data were available for derivation of AEGLs.

Mouse lethality data were used for the regression analyses of the concentration-exposure durations. Regression analysis of the relationship between time and concentration (C^n x t = k), based on four studies with the mouse, the most sensitive species, showed that n = 2. This relationship was used for all AEGL levels because the primary mechanism of action of toluene is central nervous system (CNS) depression, which at high concentrations results in death.

The AEGL-1 was based on observations of mild sensory irritation and headache in humans at a concentration of 100 ppm for up to 6 hours in an atmosphere controlled setting (Andersen et al., 1983; Rahill et al., 1996, Dick et al., 1984; Baelum et al., 1985; 1990). An uncertainty factor of 3 was chosen to protect sensitive individuals because the mechanism of action for irritation is not expected to vary greatly among individuals and no effects on ventilatory parameters were found at much higher concentrations. Extrapolation was made to the relevant AEGL time points using the relationship $C^n \times t = k$ where n = 2, based on the mouse lethality data. The endpoint and values are supported by the multiple studies with human subjects, some of which reported no effects at the 100 ppm concentration.

The AEGL-2 was based on more serious effects in humans at concentrations of ≥200 ppm for 8 hours including incoordination, dizziness, decreased reaction time, mental confusion, muscular weakness, and nausea (Wilson, 1943; von Oettingen et al., 1942). These effects were considered to represent the threshold for impaired ability to escape. An uncertainty factor of 3 was applied to account for sensitive individuals because the threshold for CNS impairment does not vary greatly among individuals. Extrapolation was made to the 10-minute, 30-minute, 1-hour and 4-hour time points using the equation $C^n \times t = k$ where n = 2 (based on mouse lethality data). The above values are supported by the behavioral effects observed in monkeys after a 50-minute exposure to 2000 ppm toluene (Taylor and Evans, 1985). At this concentration-duration, these animals exhibited significantly decreased reaction time and decreased accuracy on matching to sample tasks. Dividing the 2000 ppm concentration by intra- and interspecies uncertainty factors of 3 each (for a total of 10) results in values similar to those based on the human data.

The AEGL-3 values were derived from the exposure concentrations equal to one third of the mouse 1-hour LC_{50} reported by Moser and Balster (1985). The 1-hour mouse LC_{50} of 19,018 ppm was divided by 3 to estimate the threshold for lethality. A total uncertainty factor of 10 was applied which includes 3 to account for sensitive individuals and 3 for interspecies extrapolation (the mechanism of action for severe CNS depression does not vary greatly among individuals or

among species). The estimated 1-hour threshold for lethality of 6339 ppm was extrapolated to the 10- minute, 30-minute, 4–hour, and 8-hour AEGL-3 time points using the relationship $C^n \times t = k$ where n = 2 (calculated from the mouse lethality data). These values are supported by the accidental exposure of two men to an estimated concentration of >1842 ppm toluene for an average duration of 2.5 hours which resulted in severe but reversible CNS depression (Meulenbelt et al., 1990). Scaling of this exposure to the 10-minute, 30-minute, 1-, 4-, and 8-hour time points yields slightly higher values (2400, 1400, 970, 490, and 340 ppm, respectively) than those based on the threshold for lethality in the mouse. The proposed values are considered adequately protective since the mouse is more sensitive than humans to the CNS effects of toluene.

Summary of Proposed AEGL Values for Toluene [ppm (mg/m^3)]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL–1 (Nondisabling)	260 (980)	120 (450)	82 (300)	41 (150)	29 (112)	Eye irritation, headache in humans (Andersen et al., 1983)
AEGL–2 (Disabling)	600 (2260)	270 (1020)	190 (710)	94 (340)	67 (260)	Incoordination, mental confusion, neuro-behavioral deficits in humans (Wilson, 1943; von Oettingen et al., 1942)
AEGL–3 (Lethal)	1600 (6000)	900 (3380)	630 (2360)	320 (1200)	220 (830)	Lethality, **a** of the mouse 1-hour LC_{50} (Moser and Balster, 1985)

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1. INTRODUCTION

Toluene is a colorless liquid with a floral pungent or aromatic odor. The odor has also been described as rubbery and similar to that of moth balls (Billings and Jonas, 1981; Ruth, 1986). In 1996, world production of toluene was 12,600,000 tons. Approximately 79% of total production is from catalytic reforming of refinery streams, an additional 16% is separated from pyrolysis gasoline, and 4% is produced via separation from coal tars. However, most of the toluene produced (85-90%) is not isolated but remains as a benzene-toluene-xylene (BTX) mixture for use in gasoline. Of the remaining capacity, the primary use is for chemicals and solvents. The remainder is backblended into gasoline to increase octane ratings. In the chemical industry toluene is used as raw material in the production of benzyl chloride, benzoic acid, phenol, cresols, vinyl toluene, TNT, and toluene diisocyanate. Toluene is also used as a solvent for paints and coatings and in adhesives, inks, and pharmaceuticals. Of the total U.S. demand for chemicals, solvent use accounts for about 14% (U.S. Air Force, 1989; U.S. EPA, 1990; Ozokwelu, 1997).

For both the general population and for occupationally-exposed individuals, inhalation is the primary route of exposure to toluene. Evaporation of gasoline and automobile exhaust is the largest source of toluene in the environment, and industries that use toluene as a solvent are the second largest source (U.S. EPA, 1990). Toluene is also a common indoor contaminant due to releases from common household products and from cigarette smoke (ATSDR, 2000).

In humans and animals, the primary effect associated with inhalation exposure to toluene is central nervous system (CNS) depression. Short-term exposure of humans to 100 ppm has caused eye irritation, headache, and fatigue (Andersen et al., 1983). Acute exposures to concentrations of toluene between 200-500 ppm have produced confusion, incoordination, anorexia, and dizziness as well as impairments in reaction time, perception, and motor control (Wilson 1943). Exposures to concentrations ranging from 10,000 to 30,000 ppm have resulted in narcosis and deaths (WHO, 1985).

The chemical and physical properties of toluene are listed in Table 1.

TABLE 1. Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Toluol; phenyl methane; Methylbenzol; methyl-Benzene; Monomethyl benzene; Methacide; tolu-sol; antisal 1a	chemfinder.com, 1999
Chemical formula	C7H8	chemfinder.com, 1999
Molecular weight	92.140	chemfinder.com, 1999
CAS registry no.	108-88-3	chemfinder.com, 1999
Physical state	Clear liquid	chemfinder.com, 1999
Vapor pressure	28.7 mmHg	WHO, 1985
Vapor density (air = 1)	3.14	chemfinder.com, 1999
Specific gravity	0.867 g/cm^3	chemfinder.com, 1999
Boiling/flash point	110.6°C/4.4°C (open cup)	chemfinder.com, 1999
Solubility in water	Slightly soluble, 0.0526 g/100 mL	chemfinder.com, 1999
Odor threshold	2.9 ppm 2-40 ppm Detectable range: 0.16-37 ppm Recognition range: 1.9-69 ppm	Amoore and Hautala, 1983 Ruth, 1986 AIHA, 1989
Conversion factors in air	1 ppm = 3.75 mg/m^3 1 mg/m^3 = 0.267 ppm	ATSDR 2000

2.2. HUMAN TOXICITY DATA

2.1 Acute Lethality

An estimated 125 deaths occur per year in the United States involving solvent abuse (Winek and Collon, 1975). Very few deaths have been attributed solely to the inhalation of pure toluene. A mixture of solvents and/or a plastic bag (suffocation) was involved in most of these cases.

In 1983, Paterson and Sarvesvaran reported a fatality involving a 16-year-old Caucasian male who was found dead with a plastic bag over his head. The trachea and bronchi of the deceased contained inhaled stomach contents. His toluene blood concentration was 20.6 μg/ml and the brain and liver concentrations were 297 and 89 μg/gm tissue, respectively. The authors determined the cause of death to be toluene poisoning; they also stated that using a plastic bag to "concentrate" the vapors and direct inhalation from the bag contributed to the fatality.

In another case report (Kamijo et al., 1998), a 19-year-old woman was admitted to the emergency center with development of severe quadriparesis after prolonged (5 days) inhalation of a lacquer thinner (67% toluene, 10% ethylester oxalate, 8% butyl cellosolve, 5% butyl oxalate,

5% butanol, 5% methyl isobutyl ketone). Her neurologic evaluation revealed marked proximal dominant weakness of the extremities and deep tendon reflexes were absent. She also presented with metabolic acidosis, excessive anion gap, increased white blood cell count, and elevated hemoglobin. Her condition deteriorated drastically and her initial disorientation progressed to coma followed by death 56 hours after admission. The autopsy revealed severe renal tubular degeneration and necrosis. The cause of death was massive bilateral adrenal hemorrhage with severe degeneration and necrosis of the adrenal cortex. The authors concluded that bilateral adrenal hemorrhage should be considered when treating serious toluene intoxication with sudden clinical deterioration.

In a paper by Bass (1970), several reports of what the author characterizes as "sudden sniffing death syndrome" are described. The eyewitness accounts of the events prior to death in these case reports were similar and included 1) inhalation of volatile hydrocarbons from a bag, 2) panic, 3) physical exertion (usually running about 200 yds), and 4) sudden collapse and death. This sequalae is characterized by the author as being the result of severe cardiac arrhythmia associated with fulminate pulmonary edema, the excitement of a light plane anesthesia, hyperadrenergic crisis, or some combination of these and maybe unknown factors. The author suggests a mechanism of action involving sensitization of the myocardium by volatile hydrocarbons and subsequent physical exertion coalescing to produce sudden and severe arrhythmia.

Included in the same study by Bass (1970), the results of a nationwide survey for the frequency of solvent abuse associated with death between 1962 and 1969 were presented. He reported 110 cases of death and 10 of these involved toluene. Between 1971 and 1981, 140 deaths associated with volatile substance abuse in the United Kingdom were reported in a study by Anderson et. al, 1982. Twenty-three of these deaths were associated with toluene in solvents and adhesives.

2.2 Nonlethal Toxicity

Acute exposures have produced mild irritation and central nervous system effects. According to a literature survey (Ruth, 1986), the threshold for irritation is 200 ppm. Most studies address neurobehavioral effects. Mergler and Beauvais (1992) exposed five volunteers to 50 ppm toluene in a controlled chamber for 7 hours. Subjects were exposed for 3 consecutive days/week with an 11-day period between each 3-day session. Olfactory perception threshold, measured in decismels, were made before and after exposures. Measurements of olfactory threshold revealed a significant six-fold shift for toluene, indicating adaptation. There were significant differences between individuals, but no effect was observed for type of exposure, day, or week of assessment. The authors attributed this effect to receptor-specific saturation.

2.2.1 Case Reports

Most case reports requiring medical treatment due to acute toluene intoxication involve renal toxicity and/or metabolic acidosis, myocardial infarction, or extreme muscular weakness.

Two men working with toluene to remove excess glue from tiles in a swimming pool were exposed to >7000 mg/m^3 (>1842 ppm) of toluene in air for 2 and 3 hours, respectively

(Meulenbelt et. al, 1990). The concentration of toluene was measured at the edge of the pool by Drager tube three hours after the patients were rescued. Concentrations were presumably higher at the bottom of the pool where the men were found because toluene is heavier than air and would have sunk to the bottom of the pool where the men were found. Both men were disoriented when they were found, one was unable to walk or sit, the other was barely able to walk. Physical examinations carried out one hour after they were found revealed mucosal irritation of the eyes, slurred speech, headache, and amnesia. The patient exposed for three hours had an excessive anion gap and a sinus bradycardia. The second patient who was exposed to vapors for 2 hours, complained of headache and clinical examination revealed a sinus tachycardia and a slightly excessive anion gap. Both patients showed no abnormalities in liver function or hematological parameters. Blood toluene concentrations taken 2 hours after exposure were 4.1 and 2.2 mg/L for the three and two hour exposed patients, respectively. The most striking effect for this acute exposure was the increased anion gap in both patients which the authors attributed to either the high plasma concentration of toluene metabolites (benzoic acid and/or hippuric acid) or distal tubular acidosis. Both patients recovered without permanent or persistent effects.

Two cases of accidental occupational exposure to very high toluene concentrations were reported by Longley et al. (1967). One of the case reports involves several men who were exposed to very high concentrations of toluene in an enclosed space aboard a commercial ship. Initially, two men were assigned to spray ballast tanks with an “anti-rust” paint containing toluene. One man climbed out of the tank because he felt dizzy, and shortly after noticed that the other man had collapsed. Seventeen more men suffered symptoms of exposure during rescue operations which lasted for about 2 hours. Symptoms of exposure included unconsciousness, severe mental confusion, amnesia, and illogical behavior. All affected workers recovered fully within 30 minute after breathing oxygen, no estimate of toluene exposure concentrations was possible. The second incident also took place on a merchant ship. In this case an accidental exposure to a concentrated insecticide containing malathion 20%, piperonyl butoxide 8%, pyrethrum 1.5%, and toluene 100%. This material was mistakenly sprayed undiluted into a hold with a volume of about 102,000 cu. ft. The first operator became so confused that he was unable to understand the order to leave the hold and then was unable to climb the 30 ft. vertical ladder unassisted. Two other officers were also overcome by the fumes while trying to assist the first and four other men became intoxicated during the rescue operations. As the cholinesterase activity of the men remained at 100%, the authors felt that the malathion was not absorbed appreciably. Using a Department of Scientific and Industrial Research (DSIR) pump handle which was designed by the British Department of Scientific and Industrial Research in order to make spot determinations of hazardous atmospheres, the estimated toluene exposure concentration was 5,000 to 10,000 ppm. In addition to unconsciousness, these men also suffered nausea, incoordination, amnesia, and feelings of intoxication. Exposed persons recovered without persistent effects.

A case of myocardial infarction following an acute inhalation exposure to toluene was reported by Carder and Fuerst, 1997. A 22-year old male had been stripping varnish from the inside of a fishing boat and began to experience dizziness, vomiting, chest tightness, and difficulty breathing. He had a history of asthma which he admitted had been worsening over the past several months prior to the incident. The patient presented in the emergency room with mild respiratory distress. Liver function tests revealed elevated transaminases and the chest

examination revealed wheezing in all fields and some diffuse fine crackles. The patient was admitted and treated with oxygen, albuterol, erythromycin, cefuroxime, and IV fluids. By morning his condition had worsened due to increasing hypoxia despite oxygen support. A chest radiograph revealed pulmonary edema and the EKG results indicated a subacute lateral myocardial infarction. Once the patient was stabilized, a coronary catheterization was performed which revealed normal coronary anatomy. The authors offer several explanations for the etiology of this particular case including myocardial sensitization to hydrocarbons, the combination of albuterol and pulmonary edema, and increased susceptibility of a hydrocarbon- sensitized heart to albuterol.

Other cases involving cardiac effects as a result of toluene abuse include two case reports submitted by Wiseman and Banim (1987) and Cunningham et. al (1987). Both reports involve young boys age 15 and 16 with a history of toluene abuse. The 15-year old boy suffered clinical biventricular dilatation, a pansystolic murmur with a loud pulmonary second sound and a diastolic gallop, an enlarged heart, and low left ventricular ejection fraction. Even with diuretic, digoxin, nitrate, and salbutamol therapy, his condition worsened to the point that he was short of breath even lying down and underwent heart transplantation. The 16-year-old boy collapsed in a pool and suffered myocardial infarction and primary ventricular fibrillation secondary to coronary artery spasm after glue sniffing. He was resuscitated and recovered fully.

Renal toxicity has been described in several cases of acute toluene toxicity. Gupta et. al, 1991 report a case involving oliguric renal failure after acute exposure to a glue containing toluene. In this case a 38-year-old male had been sniffing “Pattex” and “Ashkanani” glue repeatedly for about 8 hours. He developed drowsiness, generalized weakness, nausea, vague abdominal pain, and scanty urine. A diagnosis of reversible oliguric renal failure based on the spot urinary sodium concentration of 56 mmol/L and the absence of marked proteinurea as a result of direct tubular cell injury from toluene was made. The patient also had mild impairment of liver function and evidence of severe hepatocellular injury as well as thrombocytopenia indicating bone marrow toxicity.

A similar case of renal failure after acute exposure to pure toluene was documented by Reisin et al. (1975), in this case however, the renal failure was diagnosed as non-oliguric due to severe myoglobinuria. This patient was a 49-year old man who was found unconscious 18 hours after a hose containing pure toluene had burst. The patient also suffered superficial burns over 10% of the body from contact with the toluene soaked floor and chemical pneumonitis possibly from aspirating toluene.

In another case report published by Patel and Benjamin (1986), a 32-year-old woman developed severe quadriparesis, hypokalemia, and distal renal tubular acidosis after sniffing paint (presumably toluene-based) for one week. This woman was diagnosed with severe distal renal tubular acidosis based on hyperchloremic metabolic acidosis and hypokalemia. Kamijima et al. (1994) reported a case in which a 22-year-old woman with a history of toluene abuse had sniffed approximately 6 L of toluene within one month prior to admission to the hospital. Upon examination, she was observed to have mixed hyperchloremia and high anion gap metabolic acidosis accompanied by impaired urinary acidification. A renal biopsy showed patchy areas of

tubular injury. The thinner found in the patient's room was 99 w/w% toluene and when placed in a plastic film bag, a concentration of 22,700 ppm at room temperature was measured.

Two similar case reports of renal tubular acidosis after toluene abuse were reported by Taher et. al (1974). Toluene-based (60%) paint and pure toluene were abused by a 20-year old female and a 23-year old male, respectively. Both patients were found to have toluene in their blood and the tubular acidosis was documented by metabolic acidosis (pH 7.2 to 7.3) with a normal "anion gap", hyperchloremia, and hypokalemia and high urinary pH (>6.0). The male patient continued to sniff toluene and continued to have episodes of weakness and metabolic acidosis which required medical treatment. The female had refrained from sniffing paint for 4 months after her initial admission. Several other case reports involving metabolic acidosis and hypokalemia were presented by Fischman and Oster (1979) . These cases showed high anion gap metabolic acidosis which the authors attributed to the formation of high levels of hippuric and benzoic acids with the metabolism of toluene.

In a case report by Jone et al. (1988), an unusual situation of toluene inhalation abuse and metabolic ketoacidosis is described. A 20-year-old female, who admitted to chronic use of solvents, complained of chest pain radiating to the left arm, shortness of breath, headache, occasional tachycardia, photophobia, and generalized muscle weakness as well as nausea and anorexia that had persisted for two days prior to admission. GC-MS analysis of serum samples obtained from this individual revealed high concentrations of acetoacetic acid (accounting for the large concentration of ketone bodies), as well as toluene metabolites benzoic acid and hippuric acid.

A study by King et. al, 1981 reviewed nineteen cases of acute encephalopathy due to toluene intoxication among children aged 8-14 due to toluene intoxication. These cases were observed over a six-year period. Fourteen children admitted to toluene abuse and the rest were confirmed by toluene assay. Seven of the patients had a history of euphoria and hallucinations. The other patients presented with coma (4), ataxia (3), convulsions (3), and behavior disturbance with diplopia (2). Thirteen of these children recovered completely, five of these children suffered continued psychological impairment and were lost to follow-up and one had persistent cerebellar ataxia one year after the acute episode. Persistent cerebellar ataxia was also reported in a 25-year-old man after 1 year of heavy toluene abuse (Boor and Hurtig, 1977).

Streicher et al. (1981) describe "syndromes of toluene sniffing in adults". Twenty-five patients were categorized as having one of three dominant symptom patterns: muscle weakness (Group I), gastrointestinal disorders (Group II), and neuropsychiatric disorders (Group III). Nine of these patients (Group I) presented with severe muscle weakness and in some cases quadreparesis, six patients (Group II) presented with abdominal pain, nausea, vomiting, and hematemesis, and ten patients had neuropsychiatric complaints (Group III) including: headache, dizziness, syncope, paresthesias or peripheral neuropathy, hallucinations, lethargy, cerebellar ataxia. One patient had also abused ethanol and barbituates. All these patients suffered various fluid and electrolyte imbalances including: hyperchloremia, hypobicarbonatemia, metabolic acidosis, respiratory acidosis and hypokalemia.

2.2.2 Occupational Exposures

Studies of workers exposed to toluene in an occupational setting have focused on CNS function impairment and these exposures are usually not of a magnitude required to produce serious sustained effects. Even though exact exposures (dose and time) are usually not included in these studies, they do attempt to provide information about some of the more common effects and at what concentrations these effects are observed. However, the interpretation of most occupational exposure studies is confounded by co-exposure to other solvents.

White et. al (1995) conducted a study involving screen printing workers who were acutely exposed to $\leq$ 28 ppm toluene along with other solvents used in this industry including: methyl ethyl ketone, mineral spirits, β-ether, methylene chloride, and acetic acid. All exposure levels were well below the recommended threshold limit values (TLV), 50 ppm. These workers were categorized as having high acute exposures to this solvent mix and had significantly impaired performance on tasks involving manual dexterity, visual memory, and mood when subjected to a battery of neurobehavioral tests.

An investigation of memory sequelae after an acute exposure to toluene and SBP 7 (aliphatic hydrocarbons) was pursued by Stollery and Flindt (1988). A small group of women were accidentally intoxicated by this mixture of organic solvents during an acute exposure involving adhesives used in the manufacture of tennis balls. These intoxications occurred over a period of 3 days during which time, several women experienced loss of consciousness or faintness, nausea, vomiting, and headache. Subsequently, they complained of loss of memory, personality changes with depression, and loss of confidence. The subjects were tested twice using well established memory function tests, once two months after the accident, and again six months later. They were compared to controls working within the factory who were chronically exposed to low levels and to naive unexposed controls. The results of this study indicated that the acutely exposed workers had normal performance on learning, and short-term and long-term memory tasks, although slightly lower than controls. Poor performance was observed for the acutely exposed group compared to the control on tasks that required attention division between two resource-competing tasks. There was no evidence of improvement at the follow-up testing session six months later. The authors concluded that acute solvent intoxication can result in neuropsychological sequelae lasting over eight months. Three years later in a second study by Stollery (1996) these women (8/12) were again evaluated for long term cognitive and memory dysfunction. At this evaluation, these women appeared to have impaired function on verbal tasks requiring syntactic and semantic reasoning. Chronically exposed solvent workers as well as those involved in the acute incident had difficulty with conceptually complex negative syntactic reasoning problems compared to the unexposed control group. Additionally, decision fatigue was observed following prolonged continuous choice reaction time tasks. These evaluations suggest that a single episode of solvent intoxication can result in long-term cognitive deficits.

In an early study Wilson (1943) surveyed the effects of various exposure concentrations of toluene in workers at a large industrial plant; 1,000 workers were exposed to 50 to 1500 ppm for periods of one to three weeks. Approximately 10% of the employees showed symptoms severe enough to require examination at a hospital. The employees were grouped according to the concentration of toluene fumes at their job sites as measured with a combustible gas indicator as they were referred to the hospital for treatment. In workers exposed to toluene at concentrations up to 200 ppm the most common complaints were headache, lassitude, and loss of appetite;

exposures of 200 - 500 ppm produced complaints of headache, lassitude, and anorexia that were more pronounced. These patients also complained of nausea, a bad taste in the mouth, loss of coordination, decreased reaction time, and momentary loss of memory. At > 500 ppm the major complaints were headache, nausea, dizziness, anorexia, palpitation, and extreme weakness. Upon physical examination of these patients, loss of coordination, decreased reaction time, and petechiae under the skin were observed. Laboratory investigations of these patients revealed low red blood cell counts and leukopenia, and in two of these patients a bone marrow biopsy demonstrated sequelae of aplastic anemia.

The renal function of workers exposed to toluene and xylene was evaluated by Lin Rui-cun et. al (1991). Their results showed that urinary β-microglobulin and albumin, an index for tubular and glomerular damage, respectively, were significantly higher than controls and increased progressively with exposure time. Exposure concentration was not estimated in this study. In conflict with this assessment, Nielsen et. al (1985) conducted a study involving rotogravure and flexoprint workers and naive controls. These subjects were exposed to 382 mg/m^3 (102 ppm) toluene for 6 ½ hours in a climate controlled chamber, urinary samples were taken before the exposure, at 3 hours and again at 6 hours post-exposure. No significant changes in β-microglobulin or albumin excretion rates were observed for the exposed subjects compared to the air controls.

A factory survey conducted in China using personal diffusive sampling for TWA exposure to toluene, questionnaires on subjective symptoms, hematology, serum biochemistry, hippuric acid urinary concentration, and a clinical examination including neurological evaluation revealed a dose-dependent increase in subjective symptoms among toluene-exposed workers compared to controls. The threshold concentration for symptoms at work appeared to exist at 100 ppm. At higher exposure concentrations, complaints of dizziness, floating sensations, as well as eye, nose, and/or throat irritation were associated with a significant concentration-response relationship (Ukai et. al, 1993).

A similar study was conducted by Lee et. al (1988) which included only subjects who were women in their twenties and did not consume alcohol and/or smoke on a regular basis, thus excluding several confounding factors. This study also used a questionnaire for subjective symptoms which showed a concentration-dependent increase in 64% of the symptoms compared to controls. Moreover, symptoms such as body weight loss, dimmed vision, dizziness, feelings of intoxication, headache, sore throat, and tightness in the chest showed a plateau in the range below 100 ppm and then increased again at concentrations≥ 150 ppm.

Foo et al., (1990) conducted a cross-sectional study involving 30 exposed female workers employed at an electronic assembly plant where toluene was emitted from glue. Toluene concentrations, based on personal sample monitoring were reported as 8-hour TWA. Workers were matched to a control group for age, ethnicity, and use of medications. Control workers were exposed to and average of 13 ppm and exposed workers were exposed to an average concentration of 88 ppm. The presence of other solvents was not reported. A battery of eight neurobehavioral tests administered to the workers and controls prior to the start of a workday revealed statistically significant differences in 6/8 tests, with the exposed workers performing

poorly compared with the control group. There was poor correlation between test scores and individual exposures. No further exposure information was given.

2.2.3 Experimental Studies

Several experimental studies have been conducted with normal healthy human subjects who were exposed in a controlled setting to various concentrations of toluene for varying lengths of time (Table 2). These studies have generally been concerned with identifying a threshold for subjective symptoms, such as headache or nausea, and neurobehavioral effects. Some of these studies provide information on the threshold for psychomotor dysfunction (impairment of mental traits, abilities, and processes) in humans. Several studies also addressed air quality and odor adaptation or olfactory fatigue. Additional studies with controlled human exposures to concentrations up to 200 ppm and addressing metabolism/disposition are summarized in section 4.1.

Astrand et al. (1972) exposed 15 healthy male and female subjects, ages 18-46, to concentrations of 100 or 200 ppm for 30-minute periods at rest and during exercise on a bicycle ergometer. Toluene concentrations were measured with gas chromatography. There were no differences preexposure and during exposure in heart rate, pulmonary ventilation, oxygen consumption or blood lactate content for the corresponding work loads. Differences between males and females were minor. Neurologic endpoints were not studied.

Baelum et al. (1985) reported that the acute effects of toluene exposure are slightly more pronounced for previously exposed workers (rotogravure printers) compared to previously unexposed controls. In this study, male subjects (43 printers and 43 controls), ages 29-50 years, were divided into four matched groups (control printers, exposed printers, unexposed controls and exposed controls) and exposed to either 100 ppm of toluene or clean air for 6.5 hours preceded by a 1-hour acclimatization period. The effects observed at 100 ppm for both exposed groups compared to control groups included discomfort with complaints of low air quality, strong odor, fatigue, sleepiness, a feeling of intoxication, and irritation of the eyes, nose, and throat; however, complaints increased for all subjects during the test periods (including the controls) and no annoyance was experienced. One or both groups of toluene-exposed subjects showed decreased manual dexterity in one of six tests (printers only; $p<0.10$), decreased color discrimination (both groups), and decreased accuracy in visual perception. Differences were generally no more than 25% or one standard deviation. Although no significant differences were observed between the occupationally exposed group and the naive subjects, a tendency toward greater sensitivity among occupationally exposed subjects was evident.

Healthy male subjects were exposed to successively increasing concentrations of toluene, 100, 300, 500, and 700 ppm for 20 minute duration periods. The odor of toluene was masked with menthol-crystals in this study. An increase in simple reaction time was observed at 300 ppm, at 500 ppm complex reaction time was affected, and a decrease in perceptual speed occurred at 700 ppm (Gamberale and Hultengren, 1972). This indicates that short-term exposures to toluene below 300 ppm are not associated with psychomotor dysfunction.

Winneke et al. (1974) exposed 18 human subjects to either 100 ppm toluene or control air in a controlled chamber for a 3.5 hour period. A comprehensive battery of psychomotor tests and critical flicker frequency as a measure of CNS-activation revealed no significant effects from toluene exposure.

Von Oettingen et al., (1942) conducted a study with 3 healthy human volunteers; toluene concentrations were controlled and measured by interferometric determinations. Subjects were exposed to 50, 100, 200, 300, 400, or 600 ppm for 8 hour sessions (with a ½ hour break) over the course of an 8-week period. Subjects were also exposed to 800 ppm for 3 hours then for 2 more hours following a 2 hour break. At an exposure concentration of 100 ppm, moderate fatigue and sleepiness were the only complaints. Acute exposure to toluene at a concentration of 200 ppm for 8 hours produced headache, nausea, muscular weakness, confusion, impaired coordination, and dilated pupils, as well as after-effects including fatigue, general confusion, and moderate insomnia in three humans. Higher concentrations produced effects similar to the 200 ppm exposure, however these were more severe and after effects were prolonged. Decreased red blood cell count was observed at 800 ppm. The authors also reported that there were no effects on white blood cell count or the differential count, no definite effects on blood pressure or pulse rate, and no effects were observed on respiration at any of the concentrations tested.

An evaluation of human responses to varying concentrations of toluene with a TWA of 100 ppm (with 15 minute. peaks of 300 ppm) was conducted by Baelum et al., (1990) and compared to constant toluene exposure to 100 ppm or a clean air control. Thirty-two males and 39 females were selected from a total of 507 persons comprising a random sample of the population between the ages of 31 and 50. Exposures were carried out for 7 hours in all groups and concentrations were measured using a flame ionization detector. The subjects were normal healthy males and females who did not abuse alcohol or drugs and were able to exercise for 15-minute periods with a load of 50-100 W. The toluene exposed groups complained significantly more about the poor air quality, altered temperature perception, and increased irritation in the nose and lower airways; there was a tendency toward more headache, and dizziness in the exposed groups. There was a tendency toward lower scores on vigilance tests for the toluene exposed groups compared to the control, indicating only a minimal effect on psychomotor performance as scores on other assessment tests were normal. There was not, however, a significant difference between the two toluene exposed groups.

Echeverria et al., (1989; 1991) reported on the acute neurobehavioral effects of toluene in 42 healthy college students. The toluene concentrations tested were 0, 75, and 150 ppm over a 3-day period (7 hours each day). The odor was masked with menthol (0.078 ppm) and toluene concentrations were held constant in the chamber; chamber atmospheres were measured with an infrared analyzer and confirmed by gas chromatography. A battery of performance tests (verbal, visual, and psychomotor) was administered to each participant prior to starting exposures and again at 4 and 7 hours during the exposures. The initial test served as a control for the test performed during the exposures. A 5-12% decrement in performance was considered significant if consistent with a linear trend. The results of this study included a significant decrement in performance on several tasks when subjects were exposed to 150 ppm of toluene; these included a 6.0% loss for digit span, 12.1 % for pattern recognition (latency), 5.0% for pattern memory (number correct), 6.5% for one hole, and 3% for critical tracking. These differences although statistically significant, were small and the authors concluded that based on this data a TLV of

100 ppm is probably a good estimate of the biological threshold for neurobehavioral effects. The frequency of headaches and eye irritation increased in a concentration-dependent manner as well as the number of observations of sleep during exposure. However, complaints of fatigue did not increase with increasing exposure concentrations.

The effects of toluene on nasal mucus flow, lung function (vital capacity and airway resistance), subjective response (headache and dizziness), and psychometric performance (both manual and mental tests) were evaluated during 6 hour exposures to 10, 40, or 100 ppm toluene (Andersen et al., 1983). The study was carried out using an atmosphere controlled chamber and toluene concentrations were continuously monitored using gas chromatography and photo ionization detection. Sixteen healthy male Danish students (average age 24), who were "nose breathers" volunteered for the study. Adaptation to the odor occurred, but odor was still noticeable at the higher concentrations at the end of the exposures. Three subjects reported the 100 ppm concentration as unacceptable. Lung function and nasal mucus flow were unaffected by toluene inhalation. Furthermore, toluene had no significant effects on performance of eight psychometric tasks measuring 20 different parameters; however there was a borderline significant decrease for three tests (multiplication errors, Landolt's rings, and the screw plate test) at 100 ppm. There was an increase in irritation of the eyes and nose, described as slight, and a reported decrease in air quality at 100 ppm as well as an increase in the perceived odor levels as test concentrations increased. There was no irritation of the throat or lower airways at any concentration and there was no effect on mood, fatigue, or sleepiness. However, there was an increase in the occurrence of headache, dizziness, and feeling of intoxication during the 100 ppm exposure which was described as slight to moderate and involved about half of the subjects.

A similar study by Rahill et al. (1996) employed toluene concentrations of 100 ppm or air only. Six healthy subjects performed complex psychometric and response time tasks during rest and during exercise sessions sufficient to double the ventilation rate at rest. Lung function tests were also carried out. The exposures were carried out in a large atmosphere-controlled chamber and the toluene concentration was monitored by Miran 1A infrared analyzer. The results of this study are congruent with Echeverria et al. (1991) in that latency but not accuracy during neuropsychological tests proved sensitive to 100 ppm toluene. Likewise, lung function was not affected by toluene exposure in this study. Moreover, this experiment demonstrated that physical activity can exacerbate the response to toluene as greater differences in performance were observed after exercise.

Additionally, Dick et al. (1984) found that a 4-hour exposure to 100 ppm toluene resulted in a small but significant liability on one measure out of 28 psychomotor tests. In this study 36 subjects were exposed to either placebo (a 2-minute exposure to 25 ppm toluene followed by air) or toluene at a concentration of 100 ppm in a controlled chamber. Solvent concentration was monitored using a Miran I infrared analyzer and analysis was carried out by gas chromatography every 3 minutes. A slight decrement was observed on visual-vigilance test by lowering the percentage of correct hits.

Cherry et al. (1983) found that a 4-hour exposure to 80 ppm toluene did not result in impaired performance on behavioral tasks such as performance tests, simple reaction time, choice reaction time, pursuit tracking, or visual tests. Eight male post-graduate students participated in this

experiment. Exposures were carried out in an atmosphere controlled chamber (concentration monitoring not reported) and peppermint oil was used to mask the smell of toluene.

In a similar study, 16 healthy adult male volunteers, ages 23 to 38, were exposed to 0 or 80 ppm for 4 hours (Olson et al., 1985). There were no differences in performance of tasks involving simple reaction time, short-term memory, or choice reaction time immediately after entering the exposure chamber and 2 or 4 hours into the exposure. The subjects rated the discomfort during the exposure as negligible.

Carpenter et. al (1976) reported several human and animal responses to "Toluene Concentrate," a hydrocarbon mixture produced by a large solvent manufacturer in the United States. This mixture contained butanes, pentanes, hexanes, heptanes, octanes, cyclopentanes, cyclohexanes, benzene and was 45.89 % toluene. Gas chromatographic analysis was used to monitor exposure concentrations. The odor threshold for toluene was determined to be 2.5 ppm (0.01 mg/L) in a sniff test involving two trials with six human subjects. Also from this study, a sensory threshold for toluene was determined. Six of six people indicated their willingness to work an 8 hour day in a concentration of 480 ppm toluene concentrate (220 ppm toluene), a level at which some eye irritation was reported after a 15-minute exposure. Three of these six people reported that they would be willing to work an 8 hour shift in an environment with a toluene concentrate of 930 ppm (427 ppm toluene).

TABLE 2. Neurobehavioral Effects of Toluene in Controlled Human Studies

Concentration (ppm)	Duration	Effects	Reference
40, 100	6 hours	No effect	Andersen et al., 1983
80	4 hours	No impairment of neurobehavioral tasks	Cherry et al., 1983
80	4 hours	No subjective symptoms; no impairment in tests of reaction time, short-term memory, or choice reaction time	Olson et al., 1985
100	3.5 hours	No behavioral deficits in psychomotor tests	Winneke, 1982
100	4 hours	No serious impairment in series of neuro-behavioral tests (small impairment in one measure of a visual-vigilance test)	Dick et al., 1984
100	6 hours	No significant effect on lung function (subjects exercised for 30 minutes); Slight effect on some multitask and neuro-psychological tests (increased latency but not accuracy on neurobehavioral tasks)	Rahill et al., 1996
100	6.5 hours	4 Groups tested: 2 exposed and 2 controls: sensory irritation, sleepiness, decreased performance on 4/10 tests for one or both exposure groups (manual dexterity, color discrimination, visual perception)	Baelum et al., 1985
100 300, 400, 600 800	8 hours 8 hours 3 hours	Moderate fatigue, sleepiness, headache; Increasingly severe symptoms with increasing concentrations: incoordination, nausea, confusion, dilated pupils, and extreme fatigue; Severe fatigue, nausea, confusion, incoordination, loss of self-control, bone marrow suppression	von Oettingen et al., 1942
100 300 500 700	20 minutes 20 minutes 20 minutes 20 minutes	No effect on reaction time or perceptual speed Increase in simple reaction time Increase in complex reaction time Decrease in perceptual speed- end of exposure	Gamberale and Hultengren, 1972
100 100 (TWA with peaks to 300)	7 hours (3 15-minute exercise periods)	Sensory irritation, slight decrement in one of four psychomotor performance tests; No differences in performances between constant and varying concentrations	Baelum et al., 1990
75 150	7 hours/3 days 7 hours/3 days	Mean 7% decrement in several neurobehavioral tests at 150 ppm; increases in headache, eye irritation, sleepiness	Echeverria et al., 1989; 1991

2.3 Developmental/Reproductive Toxicity

Data regarding human developmental/reproductive toxicity are restricted to chronic exposures and includes only continuous occupational and abuse situations. Intrauterine growth retardation, spontaneous abortion, premature delivery, congenital malformations, and postnatal developmental

retardation are fetal effects associated with toluene exposure; maternal effects included renal tubular acidosis and fatty liver. Further confounding these reports, social and health status variables, as well as the possibility of exposure to other fetotoxic agents (either as impurities or admixtures in toluene-containing products) and/or deliberate or accidental exposures to other chemicals or drugs are not accounted for in these reports. Unfortunately, neither exposure concentrations nor durations are reported.

Hersh et al. (1985) first described the sequalae of perinatal toluene abuse as toluene embryopathy. This syndrome was based on three children born to mothers who had regularly abused toluene throughout pregnancy. The effects of this exposure included: microcephaly, central nervous system dysfunction, attentional deficits and hyperactivity, developmental delay with greater language deficits, minor craniofacial and limb anomalies, and variable growth deficiency. In 1988, Hersh reported two new cases of toluene embryopathy in children exposed throughout pregnancy presenting with very similar clinical pathologies.

Goodwin (1988) presented five case reports involving toluene abuse during pregnancy. These five women presented with severe renal tubular acidosis from paint sniffing. Normal acid-base balance was obtained within 72 hours of treatment and cessation of toluene abuse. At birth, three of five infants suffered from intrauterine growth retardation, and two of five suffered severe anomalies and neonatal hyperchloremic acidosis. Durations of abuse ranged from 6 months to 2 years of heavy use and included most of the gestational period in all cases. Two similar cases were reported by Lindemann (1991) in which mothers had been sniffing a paint thinner composed of 66.5% toluene throughout their pregnancies. Both infants had hyperchloremic acidosis and exhibited aminoaciduria from renal tubular dysfunction. Furthermore, both infants suffered intrauterine growth retardation and had some “dysmorphic features”.

Similar effects were observed by Wilkins-Haug and Gabow (1991) who followed 21 pregnancies in ten women who had abused toluene daily for at least five years. Renal tubular acidosis in half of these women, particularly among long-term abusers, complicated the pregnancies placing the mothers at risk for hypokalemia and consequent dysrhythmias, and rhabdomyolsis. Among these pregnancies, 86 % were complicated by preterm labor, 14% resulted in a perinatal death, and 72% of the newborns suffered intrauterine growth retardation. One year later a follow-up revealed growth retardation in 61.5 % and microcephaly in 53.8%.

A case report presented by Paraf et al. (1993) describes a patient in whom fatty liver of pregnancy developed after long-term exposure to toluene in an enamel gloss and in carpet glue. A liver biopsy confirmed the diagnosis and although the mother suffered no permanent effects, the fetus was stillborn with congested viscera and placental infarction.

The pregnancy outcomes of 168 women who were occupationally exposed to organosilicone varnishes containing toluene (55 ppm) were compared to 201 non-exposed women (Syrovadko, 1977). No adverse effects were observed on fertility, course of pregnancy, or perinatal mortality. Low birth weight was observed with twice the frequency as in the control group and the incidence of asphyxia was increased as well. Evaluation of congenital effects was apparently not conducted.

Data concerning the potential human reproductive toxicity of toluene are extremely limited. A study conducted by Taskinen et al. (1989) of men occupationally exposed to organic solvents (including toluene) indicated an increase in the odds ratio of spontaneous abortion among their wives. There is some indication that dysmenorrhea may be associated with occupational exposure to toluene in women (Ng et al., 1992). However, the authors stated that it is uncertain whether other behavioral and work-related factors may also have contributed to the incidence of dysmenorrhea.

2.4 Genotoxicity

An in vitro experiment conducted by Gerner-Smidt and Friedrich (1978) showed that toluene concentrations up to of 1.52 mg/ml did not change the number of sister-chromatid exchanges (SCEs) or the number of chromosomal aberrations in human lymphocytes compared to controls. In this study, toluene did, however produce a significant cell growth inhibition compared to controls.

Male workers who were occupationally exposed only to toluene for more than 16 years were selected for analysis of chromosome aberrations and (SCE). Peripheral lymphocytes from these men were compared with unexposed controls. The exposed group had significantly more chromatid breaks, chromatid exchanges, and gaps compared to the control group (Bauchinger et al., 1982).

Five adult male volunteers were exposed to a concentration of 50 ppm for 7 consecutive hours/day for 3 days; this exposure situation was repeated three times over two weeks (Richer et al., 1993). Peripheral blood lymphocytes were evaluated for SCEs, cell cycle delay, and cell mortality. Although cell mortality was temporarily increased, disappearing after 15 hours, there were no cytogenetic effects.

2.5 Carcinogenicity

An epidemiological study conducted by Carpenter et al. (1988) compared CNS cancer deaths to controls in workers at either the Y-12 nuclear facility or Oak Ridge National Laboratory in Oak Ridge, TN. Subjects exposed for a mean period of 5 years to solvents (toluene, xylene, and methyl ethyl ketone) revealed no increased incidence in death from cancers of the CNS compared to controls. No estimation of exposure concentrations was made for this study.

A study of cancer deaths among 1595 male workers in an oil refinery who were exposed to a variety of hydrocarbons including toluene, xylene and benzene during the years of 1949-1982 was undertaken by Bertazzi et al. (1989). They found an increase in mortalities from lung and kidney cancers, brain tumors, and leukemias. There were however, no apparent trends in duration of exposure and years since first exposure which could be identified in this study.

Another study of occupational exposure to toluene was conducted involving 1020 roto-gravure printers exposed to toluene who were employed for a minimum of three months between 1925 and 1985 (Svensson et al., 1990). Estimated concentrations of toluene ranged from 450 ppm in the 1940s to as low as 30 ppm by the mid-1980s; workers were also exposed to

various concentrations of benzene and other hydrocarbons for various lengths of time. When the data were analyzed for workers who had an exposure period of at least five years and a latency of 10 years, no significant increase in deaths from cancer was observed.

It is also important to note that the International Agency for Research on Cancer (IARC) has assessed the carcinogenicity of toluene and has concluded that there is insufficient evidence to indicate carcinogenicity in humans or in experimental animals. The agency also stated that toluene is not classifiable with regard to carcinogenicity in humans (IARC, 1989).

2.6 Summary

Human deaths have been reported following exposure to high concentrations of toluene and are usually associated with intentional solvent abuse situations. Generally, these deaths have been attributed to severe renal tubular acidosis or myocardial infarction. Severe renal tubular acidosis has been described in several abuse situations and in some accidental exposures. Two men were exposed to >1842 ppm toluene vapor for 2 to 3 hours and although they were unable to walk or sit upright when they were found, they recovered completely from the metabolic acidosis and CNS effects. These men recovered without persistent untoward effects.

Healthy humans can typically tolerate up to 100 ppm without notable neurobehavioral deficits and only some mild sensory irritation after a 4-6 hour exposure. When concentrations are increased above 200 ppm, more severe effects are observed which include: headache, dizziness, incoordination, mental confusion, and fatigue. A progressive increase in reaction time was observed at 300 ppm (Gamberale and Hultengren 1972).

Other toxic effects in humans with acute inhalational exposure include renal toxicity and decreased red blood cell count. These effects occur at very high concentrations and are reversible. Developmental delay and teratogenic effects resembling fetal alcohol syndrome have been observed in humans. These incidences were the result of chronic toluene abuse during pregnancy. It is important to note that there is no evidence that this syndrome occurs in women who are occupationally exposed to toluene. The data are insufficient for cancer classification of toluene in humans at this time.

3. ANIMAL TOXICITY DATA

3.1 Acute Lethality

Acute lethality data were located for the rat and mouse. Lethal concentration data from these studies are summarized in Table 3.

3.1.1 Rats

Cameron et al. (1938) in a summary of their earlier work reported that the 6.5 hour LC_{50} for Wistar rats was approximately 12,200 ppm. Mortality was 60% (6/10) during a 1.5 hour exposure to 24,400 and all ten rats died when this exposure was extended to 6 hours. No rats died during 24-hour exposure to 6100 ppm. Rats survived 14 8-hour exposures to 1525 ppm. No details of the exposures were provided. Smyth et al. (1969) reported that 1 of 6 rats exposed to 4000 ppm for 4 hours died. No further details were provided in this range-finding study.

Groups of 10 male albino Harlan-Wistar rats were subjected to measured concentrations of Toluene Concentrate (45.89% toluene) for 4-hour exposures (Carpenter et al., 1976). A 4-hour LC_{50} for the rat was calculated at 8800 ppm. An exposure concentration of 12,000 ppm produced 100% mortality following tremors and prostration. The first mortality occurred within one hour and the remainder of the rats succumbed within 3.5 hours. Necropsy revealed lung atelectasis in 4/8 rats examined at this concentration. Animals exhibited concentration-dependent signs of toxicity during exposure including loss of coordination at 1700 ppm followed by full recovery and normal 14-day weight gains. Head tremors and prostration were observed at 6300 ppm.

In the same publication by Carpenter et al. (1976), time to death was observed using an exposure concentration of 45,000 ppm and groups of five male rats. The Lt_{50} was 11 minutes at this concentration. Progressive clinical signs included lacrimation and loss of coordination within 2 minutes followed by prostration and anesthesia within 5 minutes. No abnormal findings were observed at necropsy for these animals.

TABLE 3. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effects	Reference
rat	26,700	1 hour	LC_{50}	Pryor et al., 1978
rat	24,400 12,200 6100	1.5 hours 6.5 hours 24 hours	60% mortality 50% mortality no deaths	Cameron et al., 1938
rat	15,000	2.5 hours	80% mortality	Kojima and Kobayashi, 1973
rat	4000	4 hours	17% mortality	Smyth et al., 1969
rat	8800[a]	4 hours	LC_{50}	Carpenter et al., 1976
mouse	38,465 21,872 19,018	10 minutes 30 minutes 60 minutes	LC_{50} LC_{50} LC_{50}	Moser and Balster, 1985
mouse	24,400 12,200 6100	1.5 hours 6.5 hours 24 hours	10% mortality 100% mortality no deaths	Cameron et al., 1938
mouse	8600	3 hours	LC_{50}	Bruckner and Peterson, 1981
mouse	6940	6 hours	LC_{50}	Bonnet et al., 1979
mouse	5320	7 hours	LC_{50}	Svirbely et al., 1943

[a] Exposure was to toluene concentrate which contained 46% toluene and other hydrocarbons.

3.1.2 Mice

Cameron exposed groups of 10 mice (strain not identified) to concentrations of 6100 to 24,400 ppm for various periods of time. Mortalities were 10% and 100% following 1.5- and 6-hour exposures, respectively, to 24,400 ppm. Mortality was also 100% following a 6.5 hour exposure to 12,200 ppm. All mice survived a 24-hour exposure to 6100 ppm. No further details of the exposures were given.

Moser and Balster (1985) exposed groups of 12 male albino CD-1-mice to toluene concentrations of 2000 ppm to 5000 ppm for 10, 30, or 60 minutes. Animals were examined for lethality and behavioral toxicity (inverted screen test). The LC_{50} for each time point is presented in Table 3. The authors noted that as solvent concentrations were increased for the lethality studies, mice displayed a progression of clinical signs from excitability and hyperactivity to lethargy and hypoactivity. Shallow, rapid respiration ensued and was followed by death within 1 hour after the exposure.

Acute toxicity studies in mice conducted by Svirbely et al. (1943) revealed progressive symptoms prior to death including restlessness, muscular twitching, an S-shaped curve in the tail,

changes in respiration, incoordination, and evidence of a narcotic effect. Toluene concentrations ranged from 3000-10,000 ppm as measured by a refractometer. The 7-hour LC_{50} was 5320 ppm.

3.1.3 Rabbits

Carpenter et al., (1944) found that toluene inhalation exposures of 55000 ppm produced death in rabbits within about forty minutes over a range of about 26-62 minute. Within about 3 minute, animals were relaxed and under light anesthesia, at about 10 minute pupils were contracted and dry rales, (laryngeal, tracheal or bronchial) were evident at 11 minute. A loss of blink reflex to tactual stimulus was observed at 14 minute, and excitation (running), tremors, and chewing were noticed at about 16 minute into the exposure.

3.1.4 Cats

A group of four male cats (mixed breed) were exposed to 7800 ppm for 6 hour (Carpenter et al., 1976). Neurotoxic responses included a slight loss of coordination, mydriasis, and slight hypersensitivity to light within 20 minute. These effects progressed to ear twitching, sneezing, body jerks, and prostration within 80 minute. Increasing tremors were observed in two cats and within 2 hours all cats appeared to be under light anesthesia which lasted for the duration of the 6 hour exposure. One cat died during the subsequent 14-day observation period and the autopsy indicated pneumonia as the cause of death. Body weights were normal in three of the surviving cats, but one cat had lost 0.59 kg on the day following the exposure.

3.1.5 Dogs

Solvent abuse in humans has been associated with death from cardiac arrhythmia. Ikeda et al., (1990) examined the cardiovascular response in 25 dogs after acute inhalation exposure to toluene at 30,000 ppm for 9-10 minutes. Electrocardiogram readings revealed no changes for the first 3-4 minutes of exposure; heartbeat then became rapid for several minutes and was followed by a period of bradycardia. Ventricular fibrillation ensued shortly thereafter which was followed by death. Kobayashi et al., (1989) reported that the threshold toluene concentration for decreasing left ventricle contractility in dogs is 3800 ppm

3.2 Nonlethal Toxicity

3.2.1 Monkeys

Taylor and Evans (1985) subjected cynomolgus macaque monkeys to head-only 50 minute exposures of toluene at concentrations of 0, 100, 200, 500, 1000, 2000, 3000, and 4500 ppm and simultaneously tested for delayed matching-to-sample behavior as a measure of cognitive function. These exposures were carried out in atmosphere controlled chambers and toluene concentration was monitored continuously with an infrared gas analyzer. Cognitive function was impaired at $\geq$2000 ppm as indicated by an increase in response time and a decrease in accuracy of matching. The concentration-effect relationship was monotonic in this study.

3.2.2 Rats

Many of the nonlethal studies in rats addressed the acute CNS effects of toluene exposure. These studies are summarized in Table 4. Mullin and Krivanek (1982) tested unconditioned reflexes and conditioned reflex tasks during exposure of groups of 6 five-week-old male Charles River CD rats to concentrations of 0, 800, 1600, 3200, or 6400 ppm for 4 hours. Unconditioned reflexes consisted of locomotor activity, coordination, corneal reflex, and righting reflex. The conditioned reflex involved shock avoidance. A few rats began to fail unconditioned reflex tests at 800 ppm (one of 16 tests); the 1-, 2-, and 4-hour EC_{50} for the most sensitive test were all 1340 ppm. Decrements in conditioned avoidance were observed at 3200 ppm after exposure for 2 hours.

Male Wistar rats were exposed to 125, 250, 500, 1000, 2000, and 4000 ppm toluene in ascending order along with an air control in a study by Kishi et al. (1988). This experiment incorporated shock avoidance behavioral observations during toluene exposure. Rats were exposed to toluene or air for four hours a day and the interval between exposures was 10-20 days to avoid lingering effects. Rats were tested continuously for two hours after each exposure. When rats were exposed to 125, 250, or 500 ppm toluene, there was a decline in conditioned avoidance responses 20 minutes into the exposure compared to baseline. Rats almost completely recovered during the post-exposure period. After exposure to 1000 ppm for 4 hours or 2000 ppm for 2 hours, there were concentration-related increases in incorrect responses, acceleration of the reaction time, and decreases in the effective avoidance response rate. At the beginning of the 4000 ppm exposure, the response rate increased and gradually decreased until slight ataxia was observed.

A similar study by Wada (1997) also employed shock avoidance training as a measure of CNS impairment when rats were exposed to 2000, 4000, 6000, or 8000 ppm toluene for periods of 4 hr. As in the previous experiment, shock avoidance responses were decreased at 4000 ppm and higher, but recovery was achieved within 3-6 hours post-exposure. Also, at 2000 and at 4000 ppm locomotor activity was transiently increased. Paradoxically, at 4000 ppm response latencies were increased. The authors also reported a failure in rats exposed to 6000 or 8000 ppm to avoid electrical shock and the percentage of escape responses was increased as well. Locomotor activity was dramatically decreased at these levels, therefore, ataxia and narcosis could have contributed to impaired avoidance performance

The effects of 0.5, 1, 2, and 4 hour exposures to 150 ppm in Sprague-Dawley rats were evaluated using a multiple fixed ratio-fixed interval (FR-FI) schedule of reinforcement (Geller et al., 1979). Both schedules of reinforcement were increased during the shorter exposures (0.5 to 1 hour), showing a stimulatory effect, and decreased during the longer exposures (2 to 4 hours) compared to controls. There were considerable individual differences.

A biphasic concentration-effect relationship was observed in rats exposed to increasing concentrations of toluene by Hinman (1987). Spontaneous locomotor activity was monitored continuously in rats exposed to graded concentrations of toluene (2500, 5000, 10,000, or 15,000 ppm) for a 60-minute exposure. At 5000 ppm toluene, locomotor activity increased monophasically during exposure and subsequently decreased in the same manner during recovery. At higher exposure concentrations (10,000 to 15,000 ppm), locomotor activity initially increased, but decreased with continued exposure and eventually ceased. The highest levels of toluene

produced a biphasic recovery with time to maximum activity and time to recovery dependent upon the concentration of toluene during exposure.

A biphasic recovery curve for a variable interval response schedule was observed by Miyagawa et al. (1986). Rats were exposed to either 1700, 3400, or 5100 ppm toluene vapor for 4 hr, then response rate was assessed at recovery intervals of either 0, 30, 60, or 90 minute. At 1700 ppm, the behavioral response rate was increased by about 40% compared to baseline levels and duration of recovery period did not influence activity. A decrease in responses was observed in the 3400 ppm group at 30 minute. after exposure compared to baseline levels, but the response rate increased during the 30 - 120 period following exposure. After exposure to 5100 ppm, a decrease in responses was observed followed by a linear increase with respect to duration of recovery period. The authors also noted that at low brain toluene levels an increase in response rate occurs which is reversed at higher levels so that and inverted U-shaped curve is obtained for the relationship between lever-pressing behavior and toluene concentration in the brain.

Wood and Cox (1995) observed the biphasic nature of responses to increasing concentrations of toluene. In their study 12 rats per group were exposed to toluene concentrations at 178, 300, 560, 1000, 1780, or 3000 ppm for 2 hours during behavioral evaluation of nose-poking on a probabilistic schedule of food delivery. The authors reported biphasic concentration-effect, time-effect, and concentration-response functions at the higher concentrations. A weighted regression analysis determined that an increase of 10% in all animals would be achieved at a concentration of 182 ppm with a lower 95% confidence limit of 157 ppm. This provides a useful comparison for human experimental exposures which produce concentration-related behavioral effects at about the same concentration.

Electrophysiological studies indicate that toluene increases the wake stage and decreases the duration of the REM stage at concentrations as low as 110.6 ppm for 2 hour exposures (Gnosh et al., 1989; and Takeuchi and Hisanaga, 1977). This effect seems to be more pronounced in young rats compared to adult rats (Gnosh et al., 1990).

Other neurotoxic effects include: 2000 ppm for 2 hours produces decrease in GABA in the globus pallidus (Stengard and O'Connor, 1994); abnormal neurological signs resembling the serotonin syndrome such as hindlimb abduction, resting tremor, and head weaving as well as decreased serotonin binding in the hippocampus, pons and medulla oblongata in rats exposed to 7000 ppm toluene for 15 minute (Yamawaki et al. 1982); and Sklenovsky et al., 1989 found that rats exposed to 7909 ppm for 30 minutes had decreased levels of non-esterified fatty acids (arachidonic acid, oleic acid, and stearic acid) in the brain cortex compared to controls. The concentration of glial fibrillary acidic protein in several areas of the brain was effected by toluene exposures of 100-1000 ppm for 3 days in rats (API 1997). This effect may be a marker for toluene neuronal damage as this protein is a structural marker for astrocytes.

Larsby et al. (1986) conducted a computerized nystagmographic study in rats exposed to 1500 ppm toluene. Rats exposed to toluene showed a nystagmus reaction which lasted much longer than controls, mean velocity gain was significantly greater, and the duration of optokinetic after-nystagmus was increased compared to controls. The authors concluded that these findings were the result of toluene's effect on the cerebellum.

TABLE 4. Neurobehavioral Effects of Acute Toluene Inhalation Exposure in Rats

Concentration (ppm)	Duration	Effects	Reference
150	0.5, 1 hour 2, 4 hours	Stimulatory effect, multiple schedule performance reduced performance	Geller et al., 1979
178, 300, 560 1000, 1780 3000	2 hours 2 hours 2 hours	Increased activity (for reward) during 2 hours Increased activity, then return to control rate Increased activity, then decrease below control rate	Wood and Cox, 1995
800 1340 3200	4 hours 1 hour 2 hours	Threshold, decreased unconditioned reflex EC_{50} Most sensitive unconditioned reflex Decreased conditioned avoidance response	Mullin and Krivanek, 1982
125, 250, 500 1000, 2000 4000	4 hours 4, 2 hours 4 hours	Decrease, conditioned avoidance responses Increased incorrect responses, increased reaction time Excitation, increased response rate	Kishi et al., 1988
2000 4000 6000, 8000	4 hours 4 hours 4 hours	Increased locomotor activity Decreased conditioned avoidance responses Decreased conditioned avoidance responses, ataxia, narcosis	Wada et al., 1997
2500 5000 10,000 15,000	1 hour 1 hour 1 hour 1 hour	No effect on motor activity during exposure Increased locomotor activity Increased activity followed by slight decrease Increased activity followed by cessation of activity	Hinman, 1987

Sub-acute exposures to toluene have produced hearing loss in rats. A permanent loss of hearing in the high frequency range was observed when rats were exposed to 12000 ppm for 5-9 weeks or 1000 ppm for 2 weeks (Pryor et al., 1984; Pryor and Rebert 1992).

The acute effects of toluene inhalation on the detection of auditory signals (sensitivity index and response index) were evaluated by Bushnell et al. (1994). When rats were exposed to 0, 1000, 1500, or 2000 ppm for a duration of 1 hr., the following effects were observed: sensitivity index normally increased during sessions, however toluene eliminated this improvement; responsitivity index was decreased by toluene at the beginning of each session but returned to control levels during exposure to 1000 or 1500 ppm and within 40 minute of exposure to 2000 ppm was increased above control levels. Increases in latency proved to be concentration and time dependent.

3.2.3 Mice

Several studies in mice have focused on the neurobehavioral effects of acute toluene exposure. These studies are summarized in Table 5. Using the inverted screen test to measure motor performance, Moser and Balster (1985) exposed mice to maximum concentrations of toluene between 2000 and 5000 ppm (0-100% effect) for periods of 10, 30, 60, or 90 minute. Significantly lower EC_{50} values were obtained for each increase in exposure duration; for the 10, 30, and 60 minute exposure periods, the EC_{50} values were 2959, 2012, and 1445, respectively. The authors also presented recovery times with respect to maximum concentrations tested for each exposure duration. There was only a five minute recovery time for a 10 minute exposure at 5000 ppm. However, for the 30 and 60 minute exposures at 3000 and 2000 ppm respectively, there was a 30 minute recovery period.

Tegeris and Balster subjected groups of 8 Swiss mice to a functional observational battery (FOB) following exposure to toluene at concentrations of 0, 2000, 4000, or 8000 ppm for 20 minutes. Effects were concentration-related. Motor incoordination (abnormal gait) and decreased muscle tone and equilibrium changes as well as decreased rearing occurred at 2000 ppm. Lacrimation was observed only at 8000 ppm.

The behavioral effects of toluene exposure in mice were also evaluated by Glowa et al. (1986). A fixed-interval (FI) 60 second schedule of milk delivery after a response (breaking a beam of light) with an alternating series of 8 consecutive rewards followed by an inter-series time out of 30 minutes was developed as a means of behavioral assessment. Concentration-effect curves were constructed by exposing mice to incremental additions of toluene at 30 minute intervals. At 700 ppm the rate of response was increased and higher concentrations progressively decreased the rate of response. An EC_{50} for reducing the rate of responses was calculated to be 1657 ppm.

In a similar study by Glowa (1981), the effects of 4-hour toluene exposures for five consecutive days produced similar results. The FI 60-second milk presentation was again employed with 10 minute sessions of milk availability followed by 25 minute periods where responding had no consequences. The effects of toluene on schedule-controlled behavior were concentration-dependent: 500 ppm had little effect on the rate of responding, 1000 ppm consistently increased rates of responding, and 2000 ppm consistently decreased rates of responding.

Four different toluene exposure concentrations, 722, 785, 977, or 1193 ppm, were employed in a “behavioral despair” swimming test (rodents forced to swim in a restricted space become immobile after ~3 minutes) (De Ceaurriz et al., 1983). After 4-hour exposures, all four toluene concentrations significantly decreased the mean duration of immobility during a 3 minute test period. A concentration-effect relationship was observed with the lowest concentration of toluene producing a 31% decrease in immobility and successively increasing concentrations producing 36, 54, and 74% decreases for exposures at 722, 785, 977, or 1193 ppm, respectively.

Bruckner and Peterson (1981) exposed groups of up to 14 seven-week-old male ICR mice to concentrations of 2000, 5200, or 12,000 ppm for up to 3 hours in order to evaluate the narcotic potency, speed of onset, and duration of CNS-depressant effects of inhaled toluene. Five reflex

tests - balance, visual placing, grip strength, tail pinch, and righting reflex - were used to evaluate the onset of loss of reflexes/narcosis. Tests were performed at 5 to 15-minute intervals. Mice inhaling 12,000 ppm became depressed very rapidly and were unconscious within 15 minutes. Mice inhaling 5200 ppm became immobile within 45 minutes and unconscious at approximately 1.5 hours. Mice inhaling 2000 ppm became ataxic in 1 to 1.5 hours and, within 2 hours, were immobile in the absence of stimulation, although consciousness was not lost within the 3-hour test period. Four-week-old mice, tested separately, were slightly more sensitive to toluene-induced narcosis. Rats, tested at the same concentrations, were slightly less sensitive than mice. Separate data were not provided for rats.

In the same paper, the authors (Bruckner and Peterson, 1981), reported on recovery times of mice following 5, 10, or 20-minute exposures to concentrations of 4000, 8000, or 12,000 ppm. Minimal decrements in reflexes were observed at 4000 ppm for up to 20 minutes. Recovery to preexposure performance/reflexes took $\leq$10 minutes. Depression was greater and recovery took longer with increasing concentrations and increasing exposure durations. For example, marked depression was apparent at 5 minutes during exposure to 12,000 ppm, but full recovery took place after breathing fresh air for 10 minutes.

The effects of toluene (20 minute exposure at 2000 to 8000 ppm) were compared to the central nervous system depressant drug pentobarbital using a functional observational battery (FOB) developed for rats by Moser and adapted for mice (Tegereis and Balster, 1994). Both substances produced similar changes in measured CNS parameter including, abnormal postures, decreased arousal, increased ease of handling, and decreased rearing. High doses of pentobarbital as well as high concentrations of toluene produced mild narcosis as evidenced by flattened postures and animals lying on their sides during exposures. Rapid recovery from the CNS effects of toluene was reflected in the decreased rate of rearing during exposure which rapidly increased in the open field immediately after the 20 minute exposure. This effect was significant even at the lowest dose of toluene, 2000 ppm. Changes in gait and observations of gait abnormalities were concentration-dependent. The righting reflex was severely disrupted by toluene beginning at 2000 ppm, and the inverted screen test was significantly affected at 4000 ppm. Forelimb grip strength was decreased in a concentration-dependent manner beginning at 2000 ppm, and landing foot splay was increased at the same concentration. Toluene produced decreases in sensitivity to stimulus presentation, particularly touch and tail-pinch responses which were concentration-dependent.

The pulmonary irritation response in mice during a 30 minute exposure to several concentrations of toluene (900 - 7800 ppm) was evaluated by Nielsen and Alarie (1982). Toluene concentrations of 2600 ppm and higher produced a rapid decrease in the respiratory rate within 1 minute and then a rebound increase within the next 6 minutes to levels above the control level (stimulatory effect). The RD_{50} was 5300 ppm. In cannulated mice, only a small decrease in respiratory rate occurred at the beginning of exposures, even at the higher concentrations. The authors discuss the fading of the sensory irritation response or desensitization that occurs with some chemicals including some alkylbenzenes, making measurement of an RD_{50} difficult. The stimulatory effect was attributed to systemic absorption.

Aranyi (1985) evaluated the effects of toluene on pulmonary host defenses in mice after a single 3-hour inhalation exposure. At 500, 250, 100, and 2.5 ppm exposures to toluene, significantly decreased bactericidal activity was observed. After 5 daily 3-hour exposures to 1.0 ppm, bactericidal activity was significantly decreased, but after 20 daily 3-hour exposures, this effect was not observed.

Horiguchi and Inoue (1977) exposed mice to either 0, 1, 10, 100, or 1000 ppm for 6 hours/day for 20 days. Wheel-turning activity was increased initially but then depressed at 1 ppm after three days of exposure, activity consistently declined for all other exposure groups and plateaued at about day 14. A decrease in red blood cell count was observed in the 100 and 1000 ppm groups, a decrease in thrombocyte count was observed for the 10, 100, and 1000 ppm groups, and white blood cell count was increased in all groups after 10 days on the experiment. Recovery was complete in the 1, 10, and 100 ppm groups by day 20. A trend of hypoplasia was noticed from the bone marrow analysis in the 1000 ppm group.

TABLE 5. Neurobehavioral Effects of Acute Toluene Inhalation Exposures in Mice

Concentration (ppm)	Duration	Effects	Reference
2959 2012 1445	10 minutes 30 minutes 60 minutes	EC_{50} for inverted screen test	Moser and Balster 1985
≥2000	20 minutes	Functional observational battery changes: abnormal posture, abnormal gait, decreased arousal, decreased rearing	Tegris and Balster, 1994
500 1000 2000	4 hours 4 hours 4 hours	No effect on schedule-controlled behavior Increased rate of responding Decreased rate of responding	Glowa, 1981
1657	30 minutes	EC_{50} For decreased responding for schedule-controlled behavior	Glowa et al., 1986
722-1193	4 hours	31- 74% Decrease in immobility in “behavioral despair” swimming test	De Ceaurriz et al., 1983
2000 5200 12,000	1-1.5 hours 45 minutes 15 minutes	Ataxia, no loss of consciousness at 3 hours Immobility, loss of consciousness at 1.5 hours Loss of consciousness	Bruckner and Peterson, 1981

3.2.4 Rabbits

Kobayashi (1985) conducted an acute toluene toxicity study in rabbits using 4000 ppm in air or oxygen. The observed responses included: Cheyne-Stokes respiration, arrhythmia, increased blood pressure, and slow wave hypersynchronies in cortical and subcortical EEGs which progressed to pH and base excess level decreases and arousal reaction disappearance in the sensorimotor cortex and hippocampus. Finally, grand mal seizures were followed by postictal

depression. The respiratory acidosis shifted gradually to metabolic acidosis with continued exposure.

3.3 Developmental/Reproductive Toxicity

A developmental study in rats (API, 1993) implemented toluene inhalation exposures of 0, 750, 1500, or 3000 ppm for 6 hours/day from days 6 - 15 of pregnancy. A concentration-dependent response was observed in pregnant females at 750 ppm and above. These effects included: awareness of exposure and closed/half-closed eyelids during exposure at 750 ppm; ataxia, uncoordinated gait, decreased body weight gain during the first 2 days of the study, and hypersensitivity to noise at 1500 ppm; at 3000 ppm similar effects were observed along with abnormal limb movements, lacrimation, increased respiration, increased water consumption, decreased food consumption, and some salivation and nystabmus of the eyeball. At 1500 and 3000 ppm a minimal reduction in litter and mean fetal weights was observed as well as an increase in fetuses with reduced or unossified sternebrae.

Pregnant Wistar rats were exposed to concentrations of 0, 300, 600, 1000, or 1200 ppm toluene 6 hours/day from days 9 to 21 of gestation (Thiel and Chahoud, 1997). Dams were allowed to litter and the offspring were raised to sexual maturity. Reduced body weights of rat dams and offspring were observed in rats exposed to 1200 ppm as well as a higher incidence of mortality until weaning. Retardation of physical development was also observed in this group (incisor eruption, eye opening, and vaginal opening). No neurobehavioral differences were observed for any of the exposure groups compared to controls, and there were no differences in mating, fertility, or pregnancy indexes in the F_1 generation.

Ono et al. (1995) exposed pregnant Sprague-Dawley rats to either 600 or 2000 ppm toluene for 6 hr/day from day 7 to 17 of pregnancy. At 2000 ppm dams and offspring suffered significant body weight decreases and high fetal mortality was observed along with growth retardation compared to air controls. No internal, external or skeletal anomalies were observed and neuro-behavioral tests were not different from controls. No adverse effects were observed at the lower concentration of 600 ppm. A second study by Ono et al. (1996) examined the reproductive toxicity of toluene in male and female Sprague-Dawley rats at the same concentrations, 600 or 2000 ppm 6 hr/day. Female exposures were conducted from 14 days before gestation to day 7 of gestation and males were exposed for a total of 90 days, beginning 60 days before pairing. Neither fertility nor mating performance were affected by toluene exposure. Fetal mortality and the number of dams with dead fetuses were increased compared to controls in the 2000 ppm exposed animals. Salivation and lacrimation were observed in females during exposure to 2000 ppm and a slight decrease in body weight gain as well as a significant decrease in food consumption were noted for this group compared to controls. There were no overt observations of clinical toxicity observed in males at any exposure concentration. At necropsy, male rats exposed to 2000 ppm toluene had significantly increased kidney weights and decreased absolute and relative weights of the thymus and epididymides. Increased basophilic changes and tubular necrosis of the kidneys were evident in this group as well. Sperm count was significantly reduced in the 2000 ppm group and slightly reduced in the 600 ppm group.

Yamada (1993) exposed male rats to toluene vapor for 7 days (concentration not measured) in order to determine effects on reproductive organs. Rats were exposed to a toluene soaked cotton ball until the righting reflex was lost. This exposure produced no effect on organ weights, circulating testosterone levels, or enzyme activity.

Wistar rats were neonatally exposed to 80 ppm toluene 6 hr/day from day 1 - 7. This exposure decreased dopamine levels and utilization in the olfactory tubercle and substantia nigra of the adult rat. There was also a significant decrease in noradrenaline levels and utilization in the substantia nigra and an increase in utilization in the subependymal layer of the median eminence and in the paraventricular hypothalamic nucleus. The authors also concluded that neonatal toluene exposure diminished the responses to subacute toluene treatment in adulthood (Von Euler et al., 1989).

Mice exposed to 400 ppm toluene for 6 hr/day from days 6 -17 of gestation showed no adverse effects. At 200 ppm, an increased incidence of dilated renal pelves was noted. The relevance of this observation is ambiguous since this effect was not concentration-related and the incidence was based on the total offspring, not by litter. At the 400 ppm exposure, fetuses were more likely to have 13 ribs (normal for mice). The only effect on pregnant dams was a decreased liver-to-body weight ratio and increased LDH activity in the brain (Courtney et al., 1986).

In pregnant rabbits exposed to 100 or 500 ppm toluene for 6 hr/day from day 6 to day 18 post-insemination, no adverse effects were observed for either dams or offspring (Klimisch et al., 1992). The authors also proposed a pregnancy guidance value of 20 ppm.

3.4 Genotoxicity

Toluene has been extensively studied for genetic toxicity both in vitro and in vivo. There is an overwhelming body of evidence that indicates that toluene is not genotoxic. Very few positive studies exist and those few have confounding factors which limit their reliability and relevance (NTP, 1990).

Toluene was assayed for mutagenicity using the Ames Salmonella/microsome assay by Bos et al. (1981). In this study, toluene was unable to revert *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 either with or without metabolic activation by S9 mix derived from livers of rats either untreated or induced with Aroclor 1254. Several other studies in *Salmonella typhimurium* were also negative for gene mutation and or growth inhibition due to DNA damage (Mortelmans and Riccio, 1980; Anderson and Styles, 1978; LBI, 1978; Nestmann et al., 1980; Florin et al., 1980; Snow et al., 1981; Spanggord et al., 1982; and Haworth et al., 1983). Studies in *Bacillus subtilis* (McCarroll et al., 1981a), *Escherichia coli* (Fluck et al, 1976; McCarroll et al., 1981b; and Mortelmans and Riccio, 1980), and *Saccharomyces cerevisiae* (LBI, 1978; Mortelmans and Riccio, 1980) were also negative for genotoxic effects.

In vitro studies using mouse lymphoma L5178Y cells (LBI 1978; McGregor et al., 1988) or Chinese hamster ovary cells (Evans and Mitchell, 1980) were also negative.

Mammalian *in vivo* studies in rats have produced some positive, yet dubious results. In one inhalation study, rats that were exposed to 80 ppm toluene 4 hours/day for 4 months (Dobrokhotov and Enikeev, 1975) had an increased incidence of chromosomal aberrations. Three other oral studies in rats (Dobrokhotov, 1972; Lyapkalo, 1973; and Sina et al., 1983) also observed chromosomal aberrations or DNA single-strand breaks. However, three of these studies used toluene preparations of unspecified purity which could have been contaminated with benzene (a known clastogen). The results observed in the study by Sina et al. (1983) were probably due to cell lysis because the single-strand breaks were only observed when cytotoxicity was greater than 30% (NTP, 1990).

In vivo studies in the mouse have produced negative results. Several studies in the mouse were negative for genotoxic effects when several different parameters were evaluated. These included: micronucleus induction (Kirkhart, 1980; Gad-El-Karim et al. 1984), sperm head abnormalities (Topham, 1980), dominant lethal mutations (LBI, 1981), sister chromatid exchange (Tice et al., 1985), and chromosomal aberrations (Gad-El-Karim et al. 1984).

3.5 Carcinogenicity

There is no evidence to indicate that inhalation exposures to toluene produce increased incidences of tumors in rats or mice. Gibson and Hardisty (1983) conducted a chronic toluene inhalation study in F344 rats. The animals were exposed to 0, 30, 100, or 300 ppm toluene for 6 hours/day 5 days/week for up to two years with interim sacrifices. There was no increase in the incidences of neoplasms in treated rats compared to air controls. Since the IARC (1989) felt that these exposure levels may have been low, the NTP conducted a second series of oncogenic studies in rats and mice. These inhalation studies conducted by NTP (1990) in groups of 60 male and 60 female F344/N rats and in 60 male and 60 female B6C3F_1 mice also revealed no evidence of carcinogenicity when these animals were exposed to toluene at concentrations of 120, 600, or 1200 ppm for up to two years (6.5 hours/day, 5 days/week) compared to air controls.

3.6 Summary

Several important concepts regarding the sequalae of toluene toxicity in humans can be derived from the animal data. First, the neurobehavioral effects in animals are similar to those observed in humans with one important distinction. The rodent studies have revealed that neurotoxicity is characterized by an increase in activity (responding) then a decrease in activity (responding) until finally narcosis is observed. Unfortunately, the onset of neurobehavioral deficits are not readily observable in rodents, thus extrapolation to humans becomes more challenging.

Rodents studies have demonstrated other parallels to human toxicity. Hepatomegaly and increased serum enzyme levels as well as decreased red blood cell count and renal toxicity have been observed with prolonged exposures at high concentrations in rodents as well as in humans. The developmental delays and teratogenic effects of toluene observed in humans have also been duplicated in rodent studies. In concordance with the available human epidemiological data, evidence for carcinogenic activity of toluene as a result of inhalational exposures has not been substantiated in well conducted rodent studies.

4. SPECIAL CONSIDERATIONS

4.1 Metabolism and Disposition

As shown in controlled exposure studies with humans and animals, toluene is readily absorbed through the respiratory tract. Uptake is proportional to the concentration in the inspired air, length of exposure, and pulmonary ventilation (Astrand et al., 1972; Veulemans and Masschelein, 1978; Bruckner and Peterson, 1981). Because of the dependence of uptake on respiratory rate, uptake may be doubled or tripled during exercise compared with uptake at rest (Astrand et al., 1972; Veulemans and Masschelein, 1978; Carlsson and Lindqvist, 1977; Carlsson, 1982). In humans, dermal absorption, measured during atmospheric exposures, is ~1% of respiratory absorption (Kezic et al., 2000).

Toluene can be detected in human blood within 10-15 seconds of an exposure (), and at low concentrations reaches 60% of maximum arterial concentrations within 10-15 minutes (Benignus, 1981). However, at a concentration of 4000 ppm, arterial blood concentrations did not reach maximum values until about 2 hours after the onset of exposure (Bruckner and Peterson, 1981). Numerous studies show a correlation between atmospheric concentrations and arterial blood concentrations both in humans

Inhaled toluene is exhaled largely unchanged; however it also undergoes rapid, extensive metabolism, primarily in the liver (NTP, 1990). In mammalian species, 60-75% of the absorbed dose is converted to benzyl alcohol which is rapidly converted either directly or through the intermediate benzaldehyde to benzoic acid, a common food constituent. Following conjugation with glycine, benzoic acid is excreted in the urine as hippuric acid; smaller amounts of benzoic acid are excreted as the sulfate or glucuronide conjugate. Toluene can also be hydroxylated to form o-, m-, or p-cresol which are conjugated with sulfate or glucuronide and excreted in the urine. The cresols are minor urinary metabolites.

Inhaled toluene is largely excreted in exhaled air. Benoit et al. (1985) found that after a 90 minute exposure to 50 ppm toluene, elimination in exhaled air (83%) occurred by first order kinetics with a half-life of 27 minute. Lof et al. (1993) found that toluene elimination in the blood from 9 human volunteers after exposure to 53 ppm toluene for 2 hours was triphasic with half-lives of 3, 40, and 738 minute. Presumably, the longer half-life is representative of the mobilization of toluene from adipose tissue given its high lipophilicity. In humans there are large variations in the amounts and times of toluene metabolism, therefore, monitoring of urinary metabolites can serve only as a qualitative marker for toluene exposure (Andersen et al., 1983; Baelum et al. 1987; Hasegawa et al., 1983).

Several factors could influence rate and pathway of metabolism among humans. The cytochrome P-450 isozymes responsible for toluene metabolism influence the production of either benzyl alcohol, o-cresol, or p-cresol. There are two cytochrome P-450 isozymes which play major roles in the metabolism of toluene in rats, P-450IIC11 and P-450IIE1. The former has a high Km and becomes increasingly important with increasing exposure concentrations of toluene. The latter has a low Km and is induced by fasting and ethanol. This information has limited relevance, since humans metabolized toluene at 1.3 times the rate of rats. The action of these respective isozymes is influenced by factors such as age, sex, and pregnancy. Therefore, extrinsic

and intrinsic factors can influence the relative amounts of the various urinary metabolites that are produced after toluene exposure (Nakajima et al. 1992; ATSDR, 2000).

Ethanol consumption can inhibit the metabolism of toluene by 0.5 as compared to the urinary excretion of hippuric acid and o-cresol. This observation was made by Dossing et al. (1984) in a controlled study using healthy male subjects who were exposed to 100 ppm toluene for 7 hours while a blood alcohol level of 1% (21 mmol/L) was maintained. After the exposure, the mean alveolar toluene concentration was increased by 3.3. Also observed in this study was the lack of an influence on metabolism of toluene by two known inhibitors of microsomal enzyme activity, cimetidine and propranolol. In a study by the same authors, (Dossing et al., 1983) cigarette smoking was observed to enhance the excretion of hippuric acid and o-cresol when subjects were exposed to toluene in air.

Possible ethnic differences were revealed in a study by Inoue et al. (1986). Under similar exposure situations, male Japanese workers excreted almost twice the amount of hippuric acid compared to male Chinese workers. These differences were however, less notable between female Japanese and Chinese workers.

Exposure of 10 male and female Japanese workers, ages 18-25, to 107 ppm for 4 hours studied excretion of hippuric acid in urine samples collected hourly. (Nomiyama and Nomiyama, 1978; not in refs). Hippuric acid in urine increased from <50 mg/hour to ~125 mg/hour at the 1-hour sampling time. Excretion reached a maximum of between 175 and 200 mg/hour between the 2nd and 4th hour of exposure (there was a decrease for females during the 3rd hour) and rapidly declined following cessation of exposure.

Several researchers have reported on the uptake, distribution and elimination of toluene in controlled human studies. Some of these studies demonstrated a linear relationship between concentrations in alveolar air and arterial concentrations. Exercise increases the rate of uptake. The partition coefficient for toluene in blood/air as determined using a gas-phase vial equilibrium technique was 18 (Gargas et al., 1989).

Twenty-minute exposures to concentrations of 100, 300, 500, or 714 ppm demonstrated a linear relationship between toluene concentrations in alveolar air and arterial blood of two healthy adult male subjects (Gamberale and Hultengren, 1972). The arterial concentration reached an asymptote during the exposure to 100 ppm, but not at the higher concentrations. There were considerable differences in alveolar concentrations among 12 individuals exposed to the same concentration. In this and additional studies, times for uptake rates to reach asymptote ranged from 10 to 80 minutes.

Exposure of 12 healthy adult males to 80 ppm for 2 hours under conditions of rest resulted in alveolar and arterial and venous blood concentrations of ~19 ppm and 0.6 and 0.4 mg/kg, respectively (Carlsson, 1982). (1 mg of toluene = 11 umol) Equilibrium for all three values was reached within 30 minutes. Uptake from the lung was 50-55%. During a workload of 50 watts, alveolar air reached an equilibrium concentration of 38 ppm within 1.5 hours; arterial and venous blood concentrations at this time were 2.1 and 1.2 mg/kg. As workload increased at 30-minute intervals over the 2-hour from rest to 50 to 100 and 150 watts, concentrations of all three

parameters continued to rise over the 2-hour period and did not read equilibrium. At the end of two hours, the alveolar and arterial and venous concentrations were ~59 ppm and 3.3 and 2.7 mg/kg, respectively. Uptake decreased with increasing workload.

In a similar study, but with four 50-minute exposures interrupted by 10-minute non-exposure periods (for a total time of 240 minutes), venous blood concentrations of healthy adult male subjects reached asymptotes during the third 50-minute exposures (Veulemans and Masschelein, 1978). Peak venous blood concentrations at exposures of 50, 100, and 150 ppm were 0.2, 0.4, and 0.6 mg/L, respectively. Uptake rates increased with exercise.

Astrand et al. (1972) exposed 15 healthy male and female subjects, ages 18-46, to concentrations of 100 or 200 ppm for 30-minute periods at rest and during exercise on a bicycle ergometer. Toluene was delivered via a respiratory valve and mouthpiece. Toluene concentrations were measured in alveolar air and blood during rest and exercise on a bicycle ergometer. The concentration in alveolar air and arterial blood was of the same magnitude during exposure to 200 ppm at rest as to 100 ppm during light exercise (50-75 watts). These concentrations in alveolar air and arterial blood were 31-38 ppm and 1.95-2.25 ppm (v/v), respectively. Of the several exposure regimes, highest concentrations were attained following exposure of 2 individuals to 200 ppm with a work load of 75 watts, 51.4 and 75.0 ppm in alveolar air and 3.48 and 5.49 ppm in arterial blood. At rest, the arterial level during exposure to 100 ppm rapidly increased during the first 10-15 minutes and increased only slightly thereafter. Extension of the exposure duration to 60 minutes at rest did not change the alveolar or arterial concentrations during the last 30 minutes. Both alveolar and blood concentrations dropped rapidly postexposure.

During 4-hour exposures of eight healthy male subjects to concentrations of 53 or 80 ppm, blood (capillary) concentrations reached equilibrium at 2.5 hours and declined slightly thereafter. Blood concentrations at 2.5 hours at exposures of 53 and 80 ppm were ~4 and 6 μmol/L (0.37 and 0.55 mg/L), respectively (Wallen et al., 1985).

Blood concentrations of toluene during inhalation exposures were also studied in animal models. Bruckner and Peterson (1981) exposed groups of 4-6 six-week-old mice to concentrations of 1300 to 10,400 for various exposure durations and monitored concentrations of toluene in the blood, liver, and brain. Blood concentrations generally approached equilibrium within 1 to 1.25 hours. A 2-hour exposure to 1300 ppm resulted in a blood concentration of 97 mg/L. Following a 3-hour exposure to 4000 ppm, concentrations in the liver were highest, followed by the brain and the blood. Brain as well as blood concentrations correlated with the depth of narcosis. There was a rapid drop in liver and brain concentrations during the initial hour postexposure, with a slower decrease during the subsequent 3 hours.

Kojima and Kobayashi (1973) measured toluene in blood of rats that died. Average toluene concentrations were: brain, 890 μg/g; liver, 700 μg/g; and blood, 330 μg/g. Bruckner and Peterson (1981) measured concentrations of 40-75 μg/g in the blood of ataxic mice and concentrations of >150 μg/g in unconscious mice. There was good correlation between brain toluene concentrations and the extent of CNS depression; blood levels were also a reliable index

of the depth of narcosis. Humans experience effects at similar levels, although longer to attain level in humans due to lower breathing per kilogram of body weight.

Chapman et al. (1990) compared the metabolism and covalent binding of ^{14}C- toluene by human and rat liver microsomal fractions and liver slices. Male F344 rat liver microsomes metabolized benzene to only benzyl alcohol whereas liver microsomes from six human subjects metabolized toluene to benzyl alcohol, benzaldehyde, and benzoic acid. Microsomes from one human also metabolized toluene to p-cresol and o-cresol. The rate of toluene metabolism by human microsomes was 9-fold greater than by rat liver microsomes. Human liver microsomes required NADPH for metabolism and covalent binding did not occur in its absence. Human and rat liver slices metabolized toluene to hippuric acid and benzoic acid. The rate by human liver slices was 1.3-fold greater than by rat liver slices.

4.2 Mechanism of Toxicity

The primary toxic effects associated with toluene exposure are 1) sensory irritation, 2) CNS depression with diminished neurological responses (anesthetic effect), and 3) renal toxicity with metabolic acidosis. Three mechanisms of toxicity have been proposed: 1) Alteration of the lipid membrane ultrastructure thereby disrupting intercellular communication; 2) Interaction with the hydrophic portions of cell proteins thereby altering membrane-bound enzyme activity or receptor-site specificity; and 3) Metabolic intermediate compounds of o-cresol and p-cresol bind to cell proteins and RNA, modifying their actions (ATSDR, 2000).

Exposure to high concentrations of toluene results in feelings of euphoria which progress to lethargy and neurobehavioral deficits, these effects resemble those produced by anesthetics. Toluene is highly lipophilic and as a nonpolar, planar molecule it can behave as an anesthetic and dissolve in the interior lipid matrix of a membrane. Increasing toluene concentration produces membrane expansion as well as changes in membrane structure and fluidity. With an acute exposure toluene then diffuses out of the membrane, original integrity is regained, and functional characteristics can be restored (ATSDR, 2000).

Renal tubular acidosis is associated with very high acute or chronic toluene exposures in humans and is reversible upon termination of exposure. Batlle et. al (1988) conducted a study in the urinary turtle bladder, an epithelial analogue of the mammalian collecting tubule, to determine the mechanism of toluene-induced renal tubular acidosis. In this preparation toluene produced a decrease in the rate of H^+ secretion. Based on the results of this experiment, the mechanism proposed by the authors whereby toluene interferes with collecting tubule acidification is decreased proton conductance through the active transport pathway.

4.3 Structure-Activity Relationships

No structure activity issues have been identified with regard to toluene toxicity.

4.4 Other Relevant Information

4.4.1 Species Variability

Comparison of LC_{50} values for the rat and mouse shows little difference in sensitivity between these species. The 1-hour LC_{50} in rats was determined to be 26,700 ppm (Pryor et al., 1978). In the mouse the LC_{50} for 1 hour was 19,018 ppm as determined by Moser and Balster (1985). The sequelae of death was similar in both species with observations of lacrimation, hyperactivity, hypoactivity, lethargy, and shallow respiration followed by death. CNS depression with narcosis has also been observed in several accidental and intentional human exposures.

4.4.2 Susceptible Populations

Studies indicate that children, and particularly infants are more resistant than adults to the effects of various volatile anesthetics (Gregory, et. al., 1969; Katoh and Ikeda, et. al., 1992; Lerman et. al., 1983; Matthew, et al., 1996; Stevens, et al., 1975; and LeDez and Lerman, 1987). The susceptibility of individuals of different ages has been extensively studied in the anesthesia literature where the concentrations of various anesthetic gases in the lung which produce "anesthesia" (i.e. lack of movement) have been measured. Values are usually reported as the Minimum Alveolar Concentration (MAC) which produces lack of movement in 50% of persons exposed to that concentration. MAC's for several anesthetic gases have been measured as a function of age. The results consistently show a pattern with maximal sensitivity (lowest MAC values) in newborns, particularly prematures, pregnant women, and the elderly. The least sensitive (highest MAC values) occur in older infants, toddlers and children as compared to normal adults. The total range of sensitivity is 2-3 fold. Many organic vapors, particularly those which are strongly lipophilic, produce an anesthetic effect in exposed humans. CNS effects of these agents are thought to be additive if mixtures are involved. Toluene has produces CNS disturbances that are similar those produced by known anesthetics, therefore it would not be unreasonable to assume that the same 2-3 fold difference in sensitivity among individuals would apply for this solvent.

Little et al. (1999) conducted a study with twenty patients who were extremely sensitive to chemicals. These patients meet the definition of hypersusceptible as they were all categorized as mild to severely clinically impaired in that they were unable to work or required a major modification in their work environment in order to remain employed. These patients displayed impaired cognitive functioning characterized by degradation of long- and short-term memory and psychomotor coordination after exposure to 15 ppm toluene for 20 minutes. They also had increased T-cell binding molecules against p-aminobenzoic acid, indicating that measurement of T-cell antigen-binding molecules against chemical haptens could be useful in assessing patients who are sensitive to chemicals. The study did not use air controls.

4.4.3 Concentration-Response Relationship

When data are lacking for desired exposure times, scaling across time may be based on the relationship between acute toxicity (concentration) and exposure duration (ten Berge et al., 1986). The only data available for scaling across time are animal data. The mouse LC_{50} data were used because the mouse is slightly more sensitive to toluene exposure than the rat. Values scaled for the derivation of the 30-minute and 1-, 4-, and 8-hour timepoints were calculated from the equation $C^n \times t = k$ (ten Berge et al., 1986) where n = 2. The 10-, 30-, and 60-minute LC_{50} values calculated by Moser and Balster (1985), as well as the 3-, 6-, and 7-hour LC_{50} values calculated by Bruckner and Peterson (1981), Bonnet et al. (1979), and Svirbely et al. (1943), respectively, were used to find the least-squares linear curve fit of the graph (Appendix A, Figure 1), log time vs log LC_{50}. The resulting equation for the line was y = 5.12 - 0.51x. Since n = -1/slope, the value of the exponent n is 1.95 or 2.0.

5. DATA ANALYSIS AND PROPOSED AEGL-1

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that could produce mild odor, taste, or other sensory irritations.

5.1 Summary of Human Data Relevant to AEGL-1

Several controlled human studies have been conducted which describe the threshold level for irritation and CNS effects following acute toluene inhalation exposure. Humans begin to experience some sensory irritation accompanied by headache, mild impairment on some sensitive cognitive function tasks, and occasional slight dizziness after toluene exposures of 100 ppm for 4-6 hours (Andersen et al., 1983; Baelum et al., 1985; Baelum et al., 1990; Rahill et al., 1996; Dick et al., 1984).

The most convincing evidence for this threshold was supplied by Andersen et al., (1983). Sixteen male students were exposed to 40 or 100 ppm toluene for 6 hours with no effects at the 40 ppm exposure and only mild sensory irritation and no effects at all on psychomotor function at the 100 ppm exposure. In a study conducted by Baelum et al. (1990), 71 subjects were exposed to either 100 ppm toluene or air for 7 hours with only mild sensory effects and tendency toward more headaches and incidences of dizziness in the exposed groups. There was only a slight decrement (not significant) in performance on a vigilance test with 3 other parameters of psychomotor performance remaining unaffected. A controlled study by Echeverria et al. (1991) with the odor of toluene masked by menthol also revealed only mild sensory irritation, headache, fatigue, and slight decrements on two out of 12 neurobehavioral tasks at a toluene concentration of 150 ppm. Rahill et al., (1996) and Dick et al., (1984) also reported a slight decrement in performance on only one cognitive task after exposure to 100 ppm toluene for periods of 6 or 4 hr, respectively. Cherry et al. (1983) reported no impairment on neurobehavioral tasks after toluene exposure for 4 hours at a concentration of 80 ppm.

5.2 Summary of Animal Data Relevant to AEGL-1

There are no animal data relevant to derivation of AEGL-1.

5.3 Derivation of AEGL-1

The data of Andersen et al. (1983) were used for derivation of AEGL-1 values. At a concentration of 100 ppm only mild sensory effects were reported during a 6-hour exposure. This study along with the studies conducted by Rahill et al. (1996) and Baelum et al. (1990) support this concentration-duration relationship as the threshold for AEGL-1 level effects in humans; each of these studies report mild adverse effects at 100 ppm after 6 or more hours of continuous exposure. An extrapolation was made to the 10-, and 30-minute, 1-, 4-, and 8-hour time points using the equation $C^n \times t = k$ where n = 2, based on the mouse lethality data (see section 4.4.2). An uncertainty factor of 3 was chosen to protect sensitive individuals because the mechanism of action for irritation and headache are not expected to vary greatly among individuals. The eye irritation experienced by humans is usually characterized as "slight" even at much higher exposure concentrations than the proposed AEGL-1 values. Among humans the MAC for volatile anesthetics typically varies by about 2-3 fold; mild CNS effects like slight dizziness would be expected to occur within a similar range of variation.

AEGL-1 values are presented in Table 6. Calculations are presented in Appendix A.

TABLE 6: AEGL-1 Values for Toluene [ppm (mg/m^3)]

AEGL level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	260 (980)	120 (450)	82 (300)	41 (150)	29 (112)

There is a large body of data to support these AEGL-1 values as denoting a protective standard against the toxic effects of toluene outside those expected as defined under AEGL-1. Numerous controlled chamber studies as well as chronic exposure in the occupational setting support these conclusions.

6. DATA ANALYSIS AND PROPOSED AEGL-2

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience irreversible or other serious, long-lasting effects or impaired ability to escape. Airborne concentrations below AEGL-2 but at or above AEGL-1 represent exposure levels which may cause notable discomfort.

6.1 Summary of Human Data Relevant to AEGL-2

The best human data for use in derivation of AEGL-2 values are those of Wilson (1943) and von Oettingen et al. (1942). Wilson (1943) examined 100 employees who were occupationally exposed to toluene concentrations at 200 - 1500 ppm for periods of 1 - 3 weeks. Workers who

were exposed to concentrations of toluene between 200-500 ppm experienced headache, nausea, anorexia, lassitude, impairment of coordination and increased reaction time. Workers who were exposed to higher concentrations complained more emphatically and had more severe symptoms, however no loss of consciousness was observed at concentrations up to and including 1500 ppm.

Von Oettingen et al. (1942) exposed human volunteers to toluene at 200 ppm for 8 hrs with a 30-minute lunch break. It is unlikely that recovery would occur during this short time period because toluene is extremely lipophilic and this would prevent appreciable clearance during a brief respite. These 3 volunteers experienced mental confusion, muscular weakness, headache, nausea, paresthesias of the skin, impaired coordination, and dilated pupils with inadequate adaptation to light. All suffered after effects including insomnia, fatigue, and confusion. At higher concentrations, more severe effects were observed. Subjects who were exposed to 800 ppm for 3 hours in this study exhibited severe muscular weakness, mental confusion, lack of self-control, incoordination, and suffered after effects (nervousness and insomnia) for several days.

Gamberale and Hultengren (1972) conducted an experiment with a higher concentration (700 ppm) for a shorter duration (20 minute) in humans and noticed the same CNS threshold with increased reaction time and decreased perceptual speed which correlate well with the symptoms of mental confusion and incoordination.

6.2 Summary of Animal Data Relevant to AEGL-2

The most appropriate animal study for support in the derivation of AEGL-2 values was conducted by Taylor and Evans (1985) in cynomolgus macaque monkeys. These animals, when exposed, head only, to toluene at a concentration of 2000 ppm for 50 minute exhibited significantly impaired reaction time and matching-to-sample accuracy.

6.3 Derivation of AEGL-2

Because human data are available, these will be used for calculation of AEGL-2. The studies by Wilson (1943) and von Oettingen et al. (1942) establish that toluene concentrations at or above 200 ppm for an 8-hour exposure produce mental confusion, incoordination, lassitude, nausea and headache in humans. These employees were, however, still able to work for eight hours. Therefore, extrapolation was made to the 10-, and 30-minute, 1- and 4-hour time points using the equation $C^n \times t = k$ where n = 2 (see section 4.4.2). An uncertainty factor of 3 was applied to account for sensitive individuals because the mechanism of action for CNS effects is not expected to vary greatly between individuals. Among humans the MAC for volatile anesthetics typically varies by about 2-3 fold (see section 4.4.2); CNS effects like incoordination and mental confusion would be expected to occur within a similar range of variation. The values for AEGL-2 are given in Table 7. Calculations are presented in Appendix A.

TABLE 7: AEGL-2 Values for Toluene [ppm (mg/m^3)]					
AEGL level	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**

AEGL-2	600 (2260)	270 (1020)	190 (710)	94 (340)	67 (260)

The above values are supported by the behavioral effects observed in monkeys after a 50 minute exposure to 2000 ppm toluene (Taylor and Evans, 1985). At this concentration-duration, these animals exhibited significantly decreased reaction time and decreased accuracy on matching to sample tasks. These deficits are analogous to the threshold for more serious CNS effects in humans such as incoordination, mental confusion, and loss of memory. Dividing the 2000 ppm concentration by intra- and inter-species uncertainty factors of 3 each (for a total of 10) results in a 50 minute value of 200 ppm. Scaling to the 30 minute, 1, 4, and 8-hour time-points yields values of 258, 183, 91, and 65 ppm, respectively. These values very close to the calculated AEGL-2 values from human data.

7. DATA ANALYSIS AND PROPOSED AEGL-3

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience life-threatening effects or death. Airborne concentrations below AEGL-3 but at or above AEGL-2 represent exposure levels that may cause irreversible or other serious, long-lasting effects or impaired ability to escape.

7.1 Summary of Human Data Relevant to AEGL-3

There was one case report of accidental human exposure (Meulenbelt et al., 1990) available which was appropriate for support in derivation of AEGL-3 values. In this report two men were using toluene to remove excess glue from tiles in the bottom of a swimming pool. These men were barely conscious when they were found, they were confused and unable to walk. They also suffered paresis, eye irritation, amnesia, and had increased anion gaps presumably from the onset of distal renal tubular acidosis or the concentration of toluene's urinary metabolites, hippuric and benzoic acid. The toluene concentration measured several hours later was 1842 ppm and the duration of exposure was approximately 2.5 hours.

7.2 Summary of Animal Data Relevant to AEGL-3

Based on LC_{50} values, the mouse is the most sensitive species to the effects of toluene. Several time-points for LC_{50} values are available from the literature. Available from the literature are 10, 30, and 60 minute LC_{50} values of 38465, 21872, and 19018 ppm respectively, which were calculated for the mouse by Moser and Balster (1985) . A 6-hour LC_{50} value of 6940 ppm for the mouse was calculated by Bonnet et al. (1979) and a 7-hour LC_{50} of 5320 was calculated by Svirbely et al., 1943. Death was accompanied by severe CNS depression and respiratory failure.

7.3 Derivation of AEGL-3

The 1-hour mouse LC_{50} of 19018 ppm was divided by 3 to estimate the lowest concentration for lethality from the regression plot. This value was then used for extrapolation to the 10-minute, 30-minute, 4-hour, and 8-hour AEGL-3 time points. Values scaled for the derivation of the 30 minute, 4- and 8-hour AEGL-3 endpoints were calculated from $C^n \times t = k$ using $n = 2$ (calculated from the mouse lethality regression, section 4.4.2). A total uncertainty factor of 10 was applied which includes 3 to account for sensitive individuals and 3 for interspecies extrapolation because the mechanism of action for anesthetic effects is not expected to vary greatly between individuals (4.4.2) or among species (4.4.1), also the most sensitive species was used for the extrapolation. The values for AEGL-3 are given in Table 8. Calculations are presented in Appendix A.

TABLE 8: AEGL-3 Values for Toluene [ppm (mg/m^3)]

AEGL level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-3	1600 (6000)	900 (3380)	630 (2370)	320 (1200)	220 (830)

These values are supported by the accidental exposure of two men to >1842 ppm toluene for an average duration of 2.5 hours. Without rescue, these men might died from severe CNS depression or renal failure. Adjusting by an intraspecies uncertainty factor of 3 to protect sensitive individuals and scaling of this exposure to the 10- and 30-minute and 1-, 4-, and 8-hour time points yields values of 2400,1390, 980, 490, and 350, respectively. This exercise supports the use of the mouse $LC_{50}/3$ as the values obtained from the human accidental situation are very similar and the victims (healthy males), albeit unconscious upon discovery made a full recovery once removed from the exposure situation. The proposed values are considered adequately protective since the mouse is more sensitive than rats or humans to the CNS effects of toluene and 1/3 of the mouse LC_{50} was used as the starting point for the derivations of these numbers.

8. SUMMARY OF PROPOSED AEGLS

8.1 AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 9.

TABLE 9: Summary of AEGL Values [ppm (mg/m^3)]

AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	260 (980)	120 (450)	82 (300)	41 (150)	29 (112)
AEGL-2	600 (2260)	270 (1020)	190 (710)	94 (340)	67 (260)
AEGL-3	1600 (6000)	900 (3380)	630 (2360)	320 (1200)	220 (830)

AEGL-1 values were based on sensory irritation in humans and the AEGL-2 was based on the threshold for CNS effects in humans that might impede escape in an acute exposure situation.

The basis for AEGL-3 was a calculated 1-hour LC_{50} in the mouse. These values are considered protective because the mechanism of toxicity among humans and between species is not different.

8.2 Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures are listed in Table 10. These standards are in close agreement with the proposed AEGLs for toluene. The ACGIH (2000) recommends a TLV of 50 ppm for workers exposed continuously to toluene during a 7-8 hour workday, in a 40 hour week. The AEGL-1 for toluene is proposed at 30 ppm. OSHA (NIOSH, 1997) recommends a 10-minute maximum exposure value of 500 ppm, the proposed AEGL-2 value for a 10-minute exposure which might impede escape is 600 ppm. The NIOSH IDLH is also 500 ppm. The IDLH is based on the human data of Gamberale and Hultengren (1972), von Oettingen et al. (1942) and Wilson (1943). The ERPG (AIHA, 2000) values are also in close agreement with the proposed AEGLs. The ERPG-1 is based on controlled human studies (von Oettingen et al., 1942; Gamberale and Hultengren, 1972; Andersen et al., 1983) in which exposure to 100 ppm produced mild symptoms such as fatigue, drowsiness, headache, dizziness, and feeling if intoxication without neurotoxic effects. The ERPG-2 was based on controlled human studies in which exposure to 300 ppm for 8 hours did not result in muscular weakness or incoordination (von Oettingen et al., 1942). The ERPG-3 was based on the LC_{50} in rats (Pryor et al., 1978), divided by ~20 and the reported loss of consciousness in humans exposed to 5000 ppm for a few minutes (Longley et al., 1967). The NRC's 1-hour EEGL is 200 ppm (NRC, 19??), similar to the 1-hour AEGL-2.

Exposure limits for chronic exposures are lower than emergency guidelines. The ACGIH occupational exposure limit is 50 ppm as is the German MAK (German Research Association, 1999). The Dutch MAC is 40 ppm (Ministry of Social Affairs and Employment, 2000). The NRC's Spacecraft Maximum Allowable Concentration (SMAC; NRC, 1996) is 16 ppm for all time periods encompassing 1 hour to 180 days.

TABLE 10. Extant Standards and Guidelines for Toluene					
Guideline	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	260 ppm	120 ppm	82 ppm	41 ppm	29 ppm
AEGL-2	600 ppm	270 ppm	190 ppm	94 ppm	67 ppm
AEGL-3	1600 ppm	900 ppm	630 ppm	320 ppm	220 ppm
ERPG-1			50 ppm		
ERPG-2			300 ppm		
ERPG-3			1000 ppm		
EEGL			200 ppm		
NIOSH IDLH			500 ppm		
NIOSH REL-TWA					100 ppm
NIOSH STEL					150 ppm
OSHA peak	500 ppm				
OSHA PEL					200 ppm
OSHA Ceiling					300 ppm
ACGIH-TLV TWA					50 ppm
MAK (German)					
MAC (Dutch)					

8.3 Data Quality and Research Needs

Because toluene is a commonly used solvent, its effects on humans have been extensively studied. More than a dozen controlled studies with human subjects that addressed effects meeting the definitions of the AEGL-1 and AEGL-2 were available. The data base of neurotoxicity studies with animals is extensive, and the supporting animal data were in good agreement with the AEGL values based on the human studies. Toluene is fatal only at high concentrations. Although the data base on lethal effects was limited to rodents (rats and mice), the agreement between these two species was good. Nevertheless, the mouse was found to be slightly more sensitive than the rat to the acute effects of toluene and therefore a study with the mouse was chosen as the basis for the AEGL-3. The AEGL-3 values based on the mouse LC_{50} was supported with human data (estimated concentrations) from a serious accidental exposure that would have resulted in death without medical intervention

The neurotoxic effects and metabolism of toluene are well documented and well understood. Although specific sensitive populations were not identified, the mechanism of action of central

nervous system depression is the same for all mammalian species, and the concentration at which this effect occurs does not differ greatly among species or individuals.

Although an abundance of empirical data exists concerning the toxicity of toluene in several species (including humans), there is a lack of good concentration-effect data for exposure vs. time relationships. This exclusion is particularly prominent with respect to human exposures. While there are several well conducted, controlled, chamber studies involving human subjects, the exposure concentrations are limited to those that produce very little if any impairment or anesthetic effects in humans. However, based on the few human studies that describe effects over time and based on the fact that blood (and brain) concentrations reach equilibrium fairly rapidly, effects observed during the first hour of an exposure do not greatly increase in severity over the exposure durations relevant to AEGLs.

Several case reports and studies which describe developmental aberrations occurring as a result of toluene exposure during gestation have been reviewed in this report. In each case exposure concentrations and only approximate durations of exposure were described. These studies have failed to describe the lowest levels at which developmental anomalies can occur. The animal data available provide conflicting information about the susceptibility of children to the neurological effects of toluene. Thus, additional studies devoted to investigation of age-related effects would beneficial in evaluating differences in responses to toluene exposure among humans. Further studies on differences in metabolism, pharmacokinetics, and mechanism of action among humans would also be useful.

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APPENDIX A:
Time-Scaling Calculations for Toluene

The LC_{50} data for the mouse from the studies of Moser and Balster (1985), Bruckner and Peterson (1981), Bonnet et al. (1979), and Svirbely et al. (1943) were fit to a straight line by linear regression (Figure 1). The resulting time-scaling value of n is 1.95.

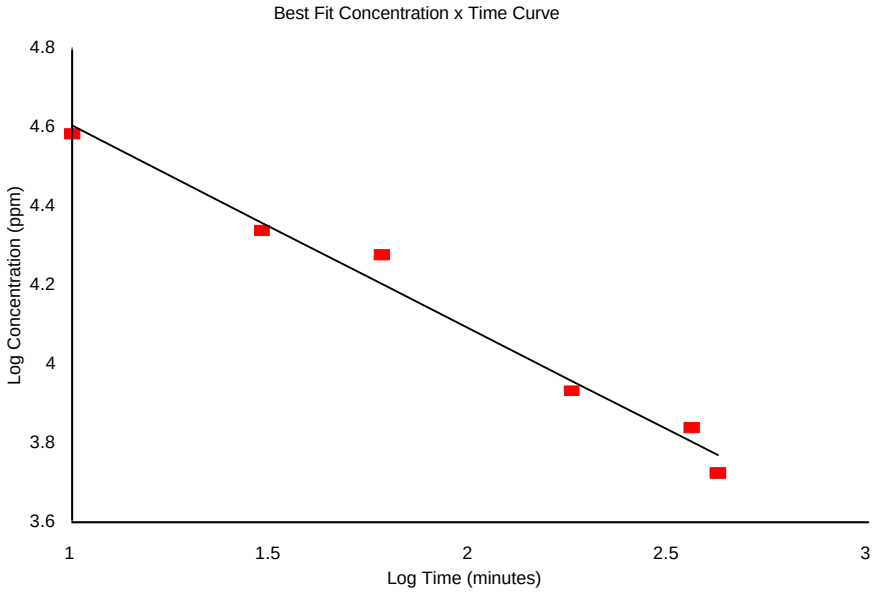

FIGURE 1. Regression curve for mouse lethality data.

Data:

Time (minutes)	Concentration (ppm)	Log time	Log concentration
10	38,465	1.0000	4.5851
30	21,872	1.4771	4.3399
60	19,018	1.7782	4.2792
180	8600	2.2553	3.9345
360	6940	2.5563	3.8414
420	5320	2.6232	3.7259

Regression Output:

Intercept	5.1193	n = 1.95
Slope	-0.5141	k = 9.1E+09
R Squared	0.9816	
Correlation	-0.9908	
Degrees of Freedom	4	
Observations	6	

APPENDIX B:
Derivation of AEGL Values

DERIVATION OF AEGL-1 VALUES

Key study: Andersen et al., 1983

Toxicity endpoint: Eye irritation, increased odor at 100 ppm for 6 hours

Uncertainty factors: 3 for intraspecies variability; subjects were healthy adult humans

Scaling: $C^2 \times t = k$ (this document, Appendix A)
$(100/3)^2 \times 6 = 6{,}667$ ppm^2·hour

Calculations:

10-minute AEGL-1
$C^2 \times 0.1$ hour = 6,667 ppm^2·hour
$C^2 = 66670$ ppm^2
C = 258 ppm

30-minute AEGL-1
$C^2 \times 0.5$ hour = 6,667 ppm^2·hour
$C^2 = 13{,}334$ ppm^2
C = 115 ppm

1-hour AEGL-1
$C^2 \times 1$ hour = 6,667 ppm^2·hour
$C^2 = 6{,}667$ ppm^2
C = 82 ppm

4-hour AEGL-1
$C^2 \times 4$ hours = 6,667 ppm^2·hour
$C^2 = 1666$ ppm^2
C = 41 ppm

8-hour AEGL-1
$C^2 \times 8$ hour = 6,667 ppm^2·hour
$C^2 = 833$ ppm^2
C = 29 ppm

DERIVATION OF AEGL-2 VALUES

Key study: Wilson, 1943

Toxicity endpoint: Headache, nausea, incoordination, decreased reaction time at 200 ppm for 8 hours

Uncertainty factors: 3 for intraspecies variability; subjects were healthy adult humans

Scaling: $C^2 \times t = k$ (this document, Appendix A)
$(200/3)^2 \times 8 = 35{,}556$ ppm^2·hour

Calculations:

10-minute AEGL-1
C^2 x 0.1 hour = 35,556 ppm^2·hour
C^2 = 355,556 ppm^2
C = 596 ppm

30-minute AEGL-1
C^2 x 0.5 hour = 35,556 ppm^2·hour
C^2 = 71,112 ppm^2
C = 267 ppm

1-hour AEGL-1
C^2 x 1 hour = 35,556 ppm^2·hour
C^2 = 35,556 ppm^2
C = 188 ppm

4-hour AEGL-1
C^2 x 4 hours = 35,556 ppm^2·hour
C^2 = 8889 ppm^2
C = 94 ppm

8-hour AEGL-1
C^2 x 8 hour = 35,667 ppm^2·hour
C^2 = 4444.5 ppm^2
C = 67 ppm

DERIVATION OF AEGL-3 LEVELS

Key study: Moser and Balster (1985)

Toxicity endpoint: The 1-hour LC_{50} of 19,018 ppm in mice was divided by 3 to obtain the threshold for lethality.

Uncertainty factors: 10: 3 for interspecies extrapolation and 3 for intraspecies variability

Scaling: $C^2 \times t = k$ (this document, Appendix A)
$(6339 \text{ ppm}/10)^2 \times 1 \text{ hour} = 401{,}871.5 \text{ ppm}^2 \cdot \text{hour}$

Calculations:

10-minute AEGL-1
$C^2 \times 0.167 \text{ hour} = 401{,}872 \text{ ppm}^2 \cdot \text{hour}$
$C^2 = 4{,}018{,}715 \text{ ppm}^2$
$C = 1600 \text{ ppm}$

30-minute AEGL-1
$C^2 \times 0.5 \text{ hour} = 401{,}872 \text{ ppm}^2 \cdot \text{hour}$
$C^2 = 803{,}743 \text{ ppm}^2$
$C = 896 \text{ ppm}$

1-hour AEGL-1
$C^2 \times 1 \text{ hour} = 401{,}872 \text{ ppm}^2 \cdot \text{hour}$
$C^2 = 401{,}872 \text{ ppm}^2$
$C = 634 \text{ ppm}$

4-hour AEGL-1
$C^2 \times 4 \text{ hours} = 401{,}872 \text{ ppm}^2 \cdot \text{hour}$
$C^2 = 100467 \text{ ppm}^2$
$C = 317 \text{ ppm}$

8-hour AEGL-1
$C^2 \times 8 \text{ hour} = 401{,}872 \text{ ppm}^2 \cdot \text{hour}$
$C^2 = 50{,}234 \text{ ppm}^2$
$C = 224 \text{ ppm}$

APPENDIX C:
Derivation Summary for Toluene AEGLs

ACUTE EXPOSURE GUIDELINES FOR TOLUENE (CAS NO. 108-88-3) DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
260 ppm	**120 ppm**	**82 ppm**	**41 ppm**	**29 ppm**

Key reference: Andersen, I., G.R. Lundqvist, L. Molhave, O.F. Pedersen, D.F. Proctor, M. Vaeth, and D.P. Wyon. 1983. Human response to controlled levels of toluene in six-hour exposures. Scand. J. Work Environ. Health. 9:405-418

Test Species/Strain/Number: Human/16 males/ Healthy students

Exposure Route/Concentrations/Durations: Inhalation/0, 10, 40, or 100, ppm /6 hours

Effects: No effects at 10 or 40 ppm; 100 ppm produced eye and nose irritation, increased perceived odor, and increased headache; no deficits were observed in a battery of eight tests measuring 20 parameters of psychomotor function (100 ppm for 6 hour was determinant for AEGL-1).

Endpoint/Concentration/Rationale: Eye and nose irritation, headache with no significant effects on psychomotor function at 100 ppm for 6 hours.

Uncertainty Factors/Rationale:
Interspecies = 1: subjects were human
Intraspecies = 3: subjects were healthy male students; no sensitive subpopulations were identified; threshold for headache and central nervous system effects does not differ greatly among individuals.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applied; insufficient data

Time Scaling: $C^n \times t = k$ where n = 2, value derived from mouse linear regression line of lethality data ranging from 10 minutes to 7 hours.

Data adequacy: A well-conducted study with human volunteers was available and the database consisting of several similar studies (preponderance of the data) supports this endpoint and level.

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
600 ppm	**270 ppm**	**190 ppm**	**94 ppm**	**67 ppm**

Key references: (1) Wilson, R.H. 1943. Toluene poisoning. J. Am. Med. Assoc. 123:1106-1108; (2) von Oettingen, W.F., P.A. Neal, D.D. Donahue, J.L. Svirbely, H.D. Baernstein, A.R. Monaco, P.J. Valor, and J.L. Mitchell. 1942. The toxicity and potential dangers of toluene with special reference to its maximal permissible concentration. U.S. Public Health Service, Public Health Bull. No. 279:1-50.

Test Species/Strain/Number: (1) Humans/100 exposed to 200-1500 ppm, gender not stated; (2) Humans/3, gender not stated

Exposure Route/Concentrations/Durations: (1) Inhalation/ 200-1500 ppm/ 8 hours/day, 1-3 weeks; (2) Inhalation/ 0, 50, 100, 200, 300, 400, or 600 ppm/ 8 hours with ½ hour lunch break and 800 ppm 3 and 2 hours with 2 hour break.

Effects: (1) <200 ppm: Headache, anorexia. 200-500 ppm; headache, nausea, dizziness, muscle incoordination, increased reaction time, loss of memory. >500 ppm: headache, nausea, dizziness, anorexia, palpitation, pronounced incoordination and extreme weakness, also bone marrow depression (2) 50 - 100 ppm; headache, drowsiness; 200 ppm: headache, nausea, incoordination, fatigue, confusion, dilated pupils with inadequate accommodation to light, also after effects including insomnia. 300-600 ppm: all the aforementioned symptoms increasing in severity with exposure concentration. 800 ppm for 3 hours produced marked symptoms of incoordination, nausea, fatigue, confusion and loss of self-control, also bone marrow depression. (200 ppm for 8 hours was determinant for AEGL-2)

Endpoint/Concentration/Rationale: (1,2) CNS effects that might impair escape: confusion, incoordination, nausea, and muscular weakness/200 ppm for 8 hours.

Uncertainty Factors/Rationale:
Interspecies = 1: Human subjects were used
Intraspecies = 3: Healthy human subjects were used; no sensitive subpopulations were identified; threshold for headache and central nervous system effects does not differ greatly among individuals.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: $C^n \times t = k$ where n = 2, value derived from mouse lethality data ranging from 10 minutes to 7 hours. Data point used for AEGL-2 derivation was 8 hours. Other time points were based on extrapolation.

Data adequacy: Two human studies (one occupational and one experimental) both support one the 200 ppm concentration. An experimental study in monkeys exposed to 2000 ppm for 50 minutes supports these values. Dividing the 2000 ppm concentration by a total uncertainty factor of 10 results in a 50-minute value of 200 ppm.

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
1600 ppm	**900 ppm**	**630 ppm**	**320 ppm**	**220 ppm**

Key reference: Moser, V.C., and R.L. Balster. 1985. Acute motor and lethal effects of inhaled toluene, 1,1,1-trichloroethane, halothane, and ethanol in mice: Effects of exposure duration. Toxicol. Appl. Pharmacol. 77:285-291.

Test Species/Strain/Sex/Number: CD-1 albino mice/ 12 males

Exposure Route/Concentrations/Durations: Inhalation: at least 3 concentrations, producing 0 - 100% effects/10, 30, or 60 minutes.

Endpoint/Concentration/Rationale: No-effect-level for death/ 6339 ppm/ threshold for death for 1 hour exposure in mice

Effects:

Concentration	LC_{50} Timepoint
38,465 ppm	10 minutes
21,872 ppm	30 minute
19,018 ppm	60 minutes

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies = 3: human and mouse data suggest little interspecies variability
Intraspecies = 3: no sensitive subpopulations were identified; threshold for central nervous system effects does not differ greatly among individuals.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: $C^n \times t = k$ where n = 2, value derived from rat lethality data ranging from 10 minutes to 7 hours. Data point used for AEGL-3 derivation was 1 hour. Other time points were based on extrapolation.

Data adequacy: The study was well-conducted with an appropriate endpoint for the AEGL-3. Human accidental exposure to an estimated concentration of 1842 ppm for 2.5 hours that would have resulted in death without medical intervention supports these values.